FAKULTAS KEDOKTERAN
PROGRAM STUDI KEDOKTERAN PROGRAM SARJANA
UNIVERSITAS YARSI

BUKU PANDUAN MAHASISWA

BLOK SISTEM HEMATOPOETIK DAN LIMFATIK

SEMESTER IV

TAHUN AKADEMIK 2021-2022

UNTUK KALANGAN SENDIRI

FAKULTAS KEDOKTERAN
UNIVERSITAS YARSI
2022

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Fakultas Kedokteran Program Studi Kedokteran Universitas YARSI

Buku Panduan Mahasiswa

Blok Sistem Hematopoetik dan Limfatik

Rencana Pembelajaran Blok (RPB)

Fakultas Kedokteran Universitas YARSI
2021 – 2022

BUKU PANDUAN MAHASISWA

BLOK HEMATOPOETIK DAN LIMFATIK

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Printed in Jakarta, Indonesia

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Dicetak di Jakarta, Indonesia

Cetakan Ketiga, Januari 2022

KATA PENGANTAR

Assalamualaikum wr.wb.

Segala puji bagi Allah SWT yang telah memberikan segala rahmat dan hidayahNya sehingga Buku Panduan Blok Sistem Hematopoetik dan limfatik bagi mahasiswa ini dapat diselesaikan penyusunannya.

Blok Sistem Hematopoetik dan limfatik ini diberikan pada semester empat yang merupakan bagian dari pemahaman sistem pembelajaran pendidikan kedokteran berbasis kompetensi di Perguruan Tinggi, khususnya di Fakultas Kedokteran Universitas YARSI. Metode belajar yang diterapkan merupakan sistem pembelajaran yang efektif untuk meningkatkan kemampuan kognitif, afektif dan psikomotor. Sumber informasi yang harus dipergunakan mahasiswa meliputi kuliah pakar, buku ajar, membaca artikel, jurnal penelitian, akses internet dan video pendidikan.

Setelah selesai mengikuti Blok Sistem Hematopoetik dan limfatik ini, mahasiswa diharapkan dapat memahami sistem tertsebut, dan menerapkan cara belajar di Perguruan Tinggi serta aspek non-medik yang meliputi aspek psikologis, sosial budaya lingkungan dan agama yang berkaitan dengan Hematopoetik dan sistem limfatik pada manusia.

Wassalamualaikum wr.wb.

Jakarta, Januari 2022

Pusat Pendidikan
Kedokteran

Fakultas Kedokteran Universitas YARSI

Visi FK Universitas YARSI

Mewujudkan Fakultas Kedokteran Islam yang bermutu tinggi yang mampu beradaptasi dengan perkembangan ilmu pengetahuan dan teknologi serta berkontribusi di bidang kedokteran dan kesehatan dalam fora nasional dan internasional pada tahun 2035.

Misi FK Universitas YARSI

1. Mengembangkan pendidikan kedokteran yang bermutu, diakui secara nasional maupun internasional, serta menghasilkan dokter muslim yang mampu beradaptasi dengan perkembangan ilmu pengetahuan dan teknologi serta berkontribusi di bidang kedokteran dan kesehatan serta mengamalkan profesinya sesuai dengan Islam.
2. Melaksanakan kajian dan penelitian yang bermutu tinggi yang diakui secara nasional maupun internasional, sesuai dengan perkembangan ilmu pengetahuan dan teknologi serta berkontribusi di bidang kedokteran dan kesehatan sesuai dengan Islam.
3. Mengembangkan pendidikan kedokteran yang bermutu, diakui secara nasional maupun internasional, serta menghasilkan dokter muslim yang mampu beradaptasi dengan perkembangan ilmu pengetahuan dan teknologi serta berkontribusi di bidang kedokteran dan kesehatan serta mengamalkan profesinya sesuai dengan Islam.
4. Melaksanakan kajian dan penelitian yang bermutu tinggi yang diakui secara nasional maupun internasional, sesuai dengan perkembangan ilmu pengetahuan dan teknologi serta berkontribusi di bidang kedokteran dan kesehatan sesuai dengan Islam.

Visi Keilmuan Program Studi

Menghasilkan Dokter Muslim bermutu tinggi yang unggul di bidang pencegahan dan komunitas, serta berkontribusi dalam meningkatkan derajat kesehatan masyarakat pada tahun 2035.

TIM PENYUSUN BUKU PANDUAN MATA KULIAH/BLOK

Penanggungjawab

Dekan : Prof. Rika Yuliwulandari, dr., M.Hlt.Sc, PhD, SpKKLP
Wakil Dekan 1 : Miranti Pusparini, dr, M.Pd(Ked)
Kaprodi Akademik : Marisa Riliani, dr., M.Biomed
Sekprodi : Rita Komalasari, dr, Ph.D
Komisi Kurikulum : Riyani Wikaningrum, dr., DMM, MSc

Penyunting

Koordiantor Blok : Werda Indriarti, dr., SpS

Penulis

Anatomi	dr. Yenni Zulhamidah, M.Sc
Histologi	dr. Aan Royhan MSc
	Kenconoviyati, S.Si. M. Biomed
Fisiologi	DR. dr. Eko Purwanto M.Kes,AIFM
	DR. dr. Diniwati Mukhtar M.Kes,AIFM
Biokimia	dr. Yulia Suciati, M.Biomed, PhD
Parasitologi	dr. Isna Indrawati, MSc
	dr. Elita Donanti, Mbiomed
	dr. Rika Ferlianti,Mbiomed
Mikrobiologi	Dr. drh. Hj. Titiek Djannatun
Farmakologi	DR. Risdawati Djohan, Apt. Mkes
Patologi Klinik	DR. dr. Anggraini Iriani, SpPK
	dr. Farida Amin, SpPK
	dr. Bambang Purwantoro, MHKes
	dr. Endah Purnamasari, SpPK
	dr. Syukrini Bahri, SpPK
Patologi Anatomi	dr. Al Ichsan, Sp.PA
Ilmu Kesehatan Anak	dr. Elsye Souvriyanti, SpA
Ilmu Penyakit Dalam	DR. dr. Faizal Drissa, SpPD., KHOM
Agama	Drs. M. Arsyad, M.Ag

DAFTAR ISI

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Jadwal kuliah

Blok Hematopoetik dan Limfatik

Deskripsi:

Blok ini bertujuan supaya mahasiswa belajar tentang konsep dasar Ilmu biomedik yang berkaitan dengan Sistem Hematopoetik dan limfatik serta pathogenesis, diagnosis, penatalaksanaan, pencegahan dan rehabilitasi gangguan sistem Hematopoetik dan limfatik didalam tubuh manusia, serta aspek non-medik yang meliputi aspek psikologis, sosial budaya lingkungan dan agama yang berkaitan dengan Sistem Hematopoetik dan limfatik pada manusia.

Capaian pembelajaran lulusan yang dibebankan pada mata kuliah/blok ini :

Kode	Capaian Pembelajaran
SIKAP (S)	
S1	Bertakwa kepada Tuhan Yang Maha Esa dan mampu menunjukkan sikap religious yang tercermin dalam nilai Universitas YARSI yaitu SCORE
S2	Menjunjung tinggi nilai kemanusiaan dalam menjalankan tugas berdasarkan agama,moral, dan etika
S3	Berkontribusi dalam peningkatan mutu kehidupan bermasyarakat, berbangsa, bernegara, dan kemajuan peradaban berdasarkan Pancasila
PENGETAHUAN (P)	
SK 3.1.P	Mampu memperjelas fenomena medis, kesehatan dan teknologi kesehatan secara ilmiah.
KETERAMPILAN UMUM (KU)	
KU 1	Mampu menerapkan pemikiran logis, kritis, sistematis, dan inovatif dalam konteks pengembangan atau implementasi ilmu pengetahuan dan teknologi yang memperhatikan dan menerapkan nilai humaniora yang sesuai dengan bidang keahliannya
KETERAMPILAN KHUSUS (KK)	
SK 2.2.K	Mampu menerapkan karakter pembelajar sepanjang hayat dalam konteks pengembangan diri
SK 3.1.K	Mampu mendemonstransikan fenomena medis, kesehatan dan teknologi kesehatan secara ilmiah
SK..4.2.P	Mampu menganalisa masalah keuangan dan penyelesaiannya (C4)

	UNIVERSITAS YARSI **FAKULTAS KEDOKTERAN** **PROGRAM STUDI KEDOKTERAN UMUM**

RENCANA PEMBELAJARAN SEMESTER

Mata Kuliah/Blok	Kode	Rumpun MK	BOBOT (SKS)	SEMESTER	Tgl Penyusunan
Sistem Hematopoetik dan limfatik	KK1104002_18	Kedokteran	6 SKS	Empat	November 2019

Capaian Pembelajaran (CP)	**CPL-PRODI**	
	S.1	Bertakwa kepada Tuhan Yang Maha Esa dan mampu menunjukkan sikap religius
	S.2	Menjunjung tinggi nilai kemanusiaan dalam menjalankan tugas berdasarkan agama,moral, dan etika
	S.3	Berkontribusi dalam peningkatan mutu kehidupan bermasyarakat, berbangsa, bernegara, dan kemajuan peradaban berdasarkan Pancasila
	KU.1	Mampu menerapkan pemikiran logis, kritis, sistematis, dan inovatif dalam konteks pengembangan atau implementasi ilmu pengetahuan dan teknologi yang memperhatikan dan menerapkan nilai humaniora yang sesuai dengan bidang keahliannya
	KU.6	Mampu memelihara dan mengembang-kan jaringan kerja dengan pembimbing, kolega, sejawat baik di dalam maupun di luar lembaganya
	SK.2..2.K	Mampu menerapkan karakter pembelajar sepanjang hayat dalam konteks pengembangan diri. (P2)
	SK.3.1.P	Mampu memperjelas fenomena medis, kesehatan dan teknologi kesehatan secara ilmiah. (C6)
	SK.3.1.K	Mampu mendemonstransikan fenomena medis, kesehatan dan teknologi kesehatan secara ilmiah.(P3)
	CP-BLOK	
	M1	Mahasiswa mampu menjelaskan konsep dasar Ilmu Biomedik pada Sistem Hematopoetik dan Limfatik
	M2	Mahasiswa mampu memahami patogenesis, penegakakan diagnosis tata laksana dan pencegahan gangguan sistem Hematopoetik dan Limfatik
	M3	Mahasiswa mampu memahami patogenesis, penegakkan diagnosis tata laksana dan pencegahan gangguan Sistem Hematopoetik dan Limfatik
	M4	Mahasiswa mampu mengenali aspek-aspek non medik yang terkait gangguan Sistem Hematopoetik dan Limfatik meliputi aspek Psikologi, sosial budaya , lingkungan dan agama
Deskripsi singkat MK/Blok	Blok ini bertujuan supaya mahasiswa mempelajari teori / konsep - konsep dasar Ilmu Biomedik yang berkaitan dengan sistem Hematopoetik dan Limfatik serta patogenesis, diagnosis, penatalaksanaan, pencegahan dan rehabilitasi gangguan	

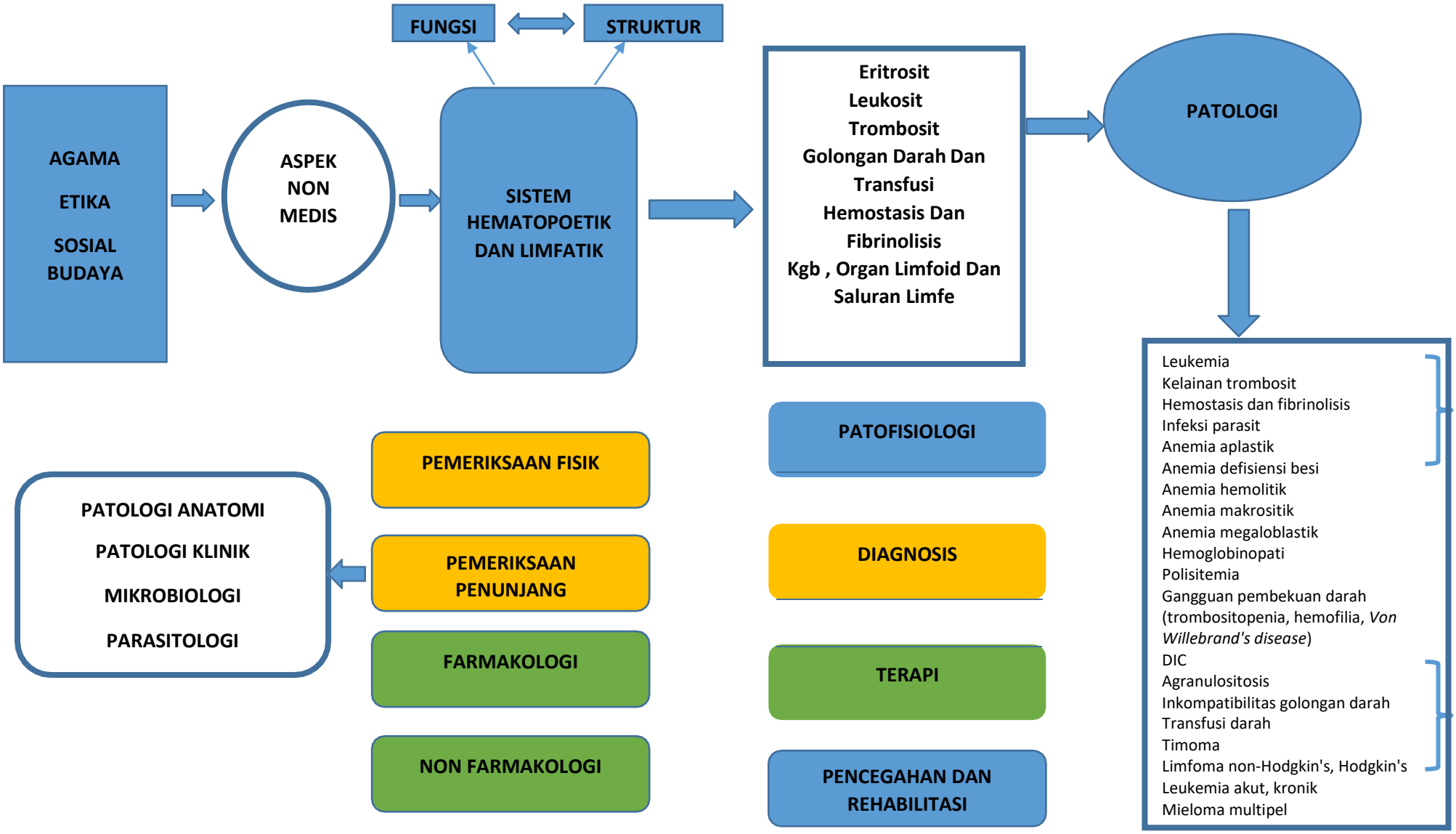
	Sistem Hematopoetik dan Limfatik didalam tubuh manuasia serta aspek non-medik yang meliputi aspek psikologis, sosial budaya lingkungan dan agama , pembelajaran dilaksanakan dengan menggunakan pendekatan SPICES. Mahasiswa diharuskan aktif mencari dan menemukan pengetahuan serta memperoleh ketrampilan dan sikap yang berkaitan dengan Sistem Hematopoetik dan Limfatik
Materi Pembelajaran/Pokok Bahasan	1. Hematopoetik 2. Anemia 3. Leukemia 4. Hemostasis dan Fibrinolisis 5. Blood bank dan golongan darah 6. Kelenjar getah bening dan salurannya 7. Kelainan pada getah bening dan limfa 8. Infeksi parasit terkait dengan darah dan limfatik 9. Agama
Pustaka	**Utama :**
	Snell, RS 1986, Anatomi Klinik, 3rd edn, EGC, Jakarta
	Mescher, Anthony, L 2013, 13th edn, Basic Histology Text and Atlas, Mc Graw Hill, New York
	Sherwood, 2016, Human Psysiology from Cells to Systems, WB Saunders, Philadelphia
	Ganong, WF 2016, 25th edn, Review of Medical Physiology, Mc Graw Hill, Boston
	Guyton, Hall, 2016, 13th edn, Textbook of medical physiology, Elsevier Inc, Philadelphia
	Martini, FH 2014, 6th Edn, Fundamentals of Anatomy and Physiology, Pearson Education Int, UK
	Sherwood, L 2017, 9th edn, From Cells to System. Human Physiology, Brooks Cole Thomson Learning Inc, Belmont, USA
	Sherman, VL 2015, 7th edn, The Mechanisms Of Body Function. Human Physiology, Mc Graw Hill, NewYork
	Murray, RK 2000, 25th edn, Erytrocites and Leukocites, dalam Harper's Biochemistry, Appleton & Lange, England
	Diggs, Bell, S 2007, 7th edn, The morphology of human blood cells, Abbott Laboratories, illinois
	McKenzie, SB 1999, 2nd edn, Textbook of hematology, William & Wilkins, Philadelphia
	Cotran, RS, Kumar, V, Robbins, SL 2007, 7th 7th edn, Robbins pathologic basic of disease, WB Saunders, Philadelphia
	Wintrobe, 2002, 13th edn, Clinical Hematology, Lea & Febiger, Philadelphia
	Hardman, JG, Limbird, LE 1996, 9th edn, Goodman Gillman's The Pharmacological Basic of Therapeutics, Mosby, Philadelphia
	Hoffbrand, AV, Moss, PAH 2016, 7th edn, Hoffbrands Essential Hematology, John Wiley & Sons Ltd, New Jersey Bain, BJ 2015, 5th edn, Blood cell: a practical guide, John Wiley & Sons Ltd, New Jersey
	Rahajuningsih, D, Setiabudy, 2018, 6th edn, Hemostasis dan Trombosis, BP FKUI, Jakarta
	World Health Organization, 2010, Hand book The clinical use of Blood, WHO, Geneva

	Rosmiati, H, Gan, VHS 1997, Antikoagulan, Antitrombotik, Trombolitik dan Hemostasis, dalam Farmakologi dan Terapi, FKUI, Jakarta
	Wardhani, S, Rosmiati, H 2007, 5th edn, Antianemia defisiensi, dalam Farmakologi dan Terapi, FKUI, Jakarta
	De Braun, Vichinsky, E 2007, 18th edn, Nelson Textbook of Pediatrics, Thallassemia Syndrome, Elsevier, Philadelphia
	Permono, B, Ugrasena, IDG 2006, 2nd edn, Talassemia, dalam Buku Ajar Hematologi Anak, Penerbit Ikatan Dokter Anak Indonesia, Jakarta
	Soeparman, Wasadji, S 2006, 4th edn, Hematologi, dalam Buku Ajar Ilmu Penyakit Dalam, FKUI, Jakarta
	Pendukung :
	Harrison's Principles of Internal Medicine 2015, McGraw Hill, New York
	Behrman, RE, Kleigman, EM, Jenson, HB 2016, Nelson Textbook of Pediatrics, Elsevier Scientific, Philadephia

Media Pembelajaran	**Perangkat lunak:**	**Perangkat keras:**
	Media elektronik	Buku teks Buku ajar Jurnal Buku referensi lainnya Ruang tutorial Lab anatomi,Lab Histo,PK,PA

Team Blok	Anatomi, Histologi, Fisiologi, Biokimia, Parasitologi, Mikrobiologi, Patologi Anatomi, Patologi Klinik, Farmakologi, Ilmu Kesehatan Anak, Ilmu Penyakit Dalam, Agama
Matakuliah syarat/blok terkait	Blok prinsip biomedik1,Blok prinsip biomedik 2,Blok Homeostasis dan cairan,Blok Mekanisme Penyakit 1,Blok Mekanisme Penyakit 2,Blok Mekanisme Pertahanan Tubuh

PETA KONSEP


FUNGSI
STRUKTUR
AGAMA
ETIKA
SOSIAL BUDAYA
ASPEK NON MEDIS
SISTEM HEMATOPOETIK DAN LIMFATIK
Eritrosit
Leukosit
Trombosit
Golongan Darah Dan Transfusi
Hemostasis Dan Fibrinolisis
Kgb , Organ Limfoid Dan Saluran Limfe
PATOLOGI
Leukemia
Kelainan trombosit
Hemostasis dan fibrinolisis
Infeksi parasit
Anemia aplastik
Anemia defisiensi besi
Anemia hemolitik
Anemia makrositik
Anemia megaloblastik
Hemoglobinopati
Polisitemia
Gangguan pembekuan darah (trombositopenia, hemofilia, Von Willebrand's disease)
DIC
Agranulositosis
Inkompatibilitas golongan darah
Transfusi darah
Timoma
Limfoma non-Hodgkin's, Hodgkin's
Leukemia akut, kronik
Mieloma multipel
PATOFISIOLOGI
DIAGNOSIS
TERAPI
PENCEGAHAN DAN REHABILITASI
PEMERIKSAAN FISIK
PEMERIKSAAN PENUNJANG
FARMAKOLOGI
NON FARMAKOLOGI
PATOLOGI ANATOMI
PATOLOGI KLINIK
MIKROBIOLOGI
PARASITOLOGI

CAPAIAN PEMBELAJARAN BLOK

CP BLOK	SUB-CP BLOK	INDIKATOR
1. Memahami anatomi sistem lymphatic dan organ lymphoid	1.1 Memahami dan mengetahui Sistem Lymphaticus (pembuluh lymph ,nodus lymphaticus)	1.1.1. Mengetahui pengertian dan aliran lymph 1.1.2. Mengetahui pengertian, letak dan struktur pembuluh lymph 1.1.3. Mengetahui pengertian, letak dan struktur nodus lymphaticus
	2.1 Memahami dan mengetahui Organ Lymphoid (Tonsil,Thymus, Lien)	2.1.1. Mengetahui klasifikasi, letak, struktur, vascularisasi dan inervasi Tonsil 2.1.2. Mengetahui letak, struktur, vascularisasi dan inervasi Thymus 2.1.3. Mengetahui letak, struktur, vascularisasi dan inervasi Lien
2. Mahasiswa mampu memahami teori/konsep-konsep dasar ilmu biomedik pada histologi darah dan hematopoietik	2.1 Mengenal susunan mikroskopis 2.2 Mengenal hematopoiesis	3.1.1. Menjelaskan nomenklatur dan susunan mikroskopis eritrosit 3.1.2. Menjelaskan nomenklatur dan susunan mikroskopis dan mengidentifikasi jenis – jenis leukosit bergranula spesifik dan leukosit tidak bergranula spesifik 3.1.3. Menjelaskan nomenklatur dan susunan mikroskopis keping darah 3.1.4. Menjelaskan Teori Hematopoiesis 3.1.5. Menjelaskan eritropoiesis 3.1.6. Menjelaskan granulopoiesis 3.1.7. Menjelaskan trombopoiesis 3.1.8. Menetapkan dengan mikroskop cahaya: - Eritrosit - Eosinofil - Basofil - Limfosit - Monosit - Trombosit

4. Mahasiswa mampu memahami teori/konsep dasar ilmu biomedik pada histologi jaringan limfoid	4.1. Mengenal susunan mikroskopis jaringan limfoid 4.2. Mengenal sel-sel darah yang berperan dalam sistem imun 4.3. Mengenal susunan mikroskopis pembuluh limf	4.1.1. Menjelaskan susunan mikroskopis organ limfoid primer : thymus 4.1.2. Menjelaskan susunan mikroskopis organ limfoid sekunder : lien, limfonodus 4.1.3. Menjelaskan susunan mikroskopis dan lokasi MALT (mucous associated lymphoid tissue) : tonsila, plaque peyeri 4.1.4. Menjelaskan dan mengidentifikasi sel-sel darah yang berperan dalam sistem imun 4.1.5. Menetapkan dengan mikroskop cahaya perbedaan histologis organ – organ limfoid 4.1.6. Menetapkan dengan mikroskop

		cahaya : limfosit, sel retikulum, sel plasma, makrofag 4.1.7. Menjelaskan susunan mikroskopis kapiler limf, pembuluh limf sedang dan besar 4.1.8. Menjelaskan perbedaan susunan mikroskopis pembuluh limf dengan pembuluh darah arteri dan vena 4.1.9. Menetapkan dengan mikroskop cahaya susunan mikroskopis pembuluh limfe
5. Memahami fungsi darah	5.1. Memahami fungsi respirasi, transportasi, nutrisi, ekskresi, kekebalan, dan pengaturannya	5.1.1. Mengidentifikasi komponen darah 5.1.2. Mengidentifikasi fungsi resprasi 5.1.3. Mengidentifikasi fungsi ekskresi 5.1.4. Mengidentifikasi fungsi transportasi 5.1.5. Mengidentifikasi fungsi nutrisi 5.1.6. Mengidentifikasi fungsi kekebalan
	5.2. Memahami plasma dan elemen seluler darah	5.2.1. Mengidentifikasi plasma 5.2.2. Mengidentifikasi sel darah merah, sel darah putih dan trombosit 5.2.3. Mengidentifikasi hematopoiesis 5.2.4. Mengidentifikasi regulasi hematopoiesis
6. Memahami eritropoiesis, leukopoiesis dan regulasinya	6.1. Memahami eritropoiesis, leukopoiesis	6.1.1. Menjelaskan eritropoiesis 6.1.2. Menjelaskan fungsi hemoglobin 6.1.3. Menjelaskan sintesis hemoglobin 6.1.4. Menjelaskan peran eritopoietin, Vitamin B12, faktor instrinsik 6.1.5. Menjelaskan stimulasi dan regulasi leukopoiesis
7. Memahami dan menjelaskan gangguan eritrosit	7.1. Memahami anemia dan polisitemia	7.1.1. Menyebutkan jenis-jenis anemia 7.1.2. Menjelaskan masing-masing penyebab anemia 7.1.3. Menjelaskan penyebab polisitemia

8. Memahami siklus hidup eritrosit	8.1. Memahami masa hidup eritrosit	8.1.1. Menjelaskan masa hidup eitrosit sekitar 120 hari 8.1.2. Menjelaskan peran hati dalam pembentukan biirubin
9. Menguasai konsep-konsep dasar ilmu Fisiologi yang berkaitan dengan hematopoetik & limfatik.	9.1. Mahasiswa mampu menjelaskan fisiologi hemostasis.	9.1.1. Mampu menjelaskan proses hemostasis 9.1.2. Mampu menyebutkan peran factor pembekuan darah 9.1.3. Mampu menjelaskan jalur pembekuan ekstrinsik & intrinsic 9.1.4. Mengetahui dampak penyimpangan hemostasis berupa thrombosis intravascular 9.1.5. Mampu menjelaskan proses fibrinolysis 9.1.6. Memahami fungsi dan peranan komponen fibrinolisis
10. Memahami konsep-konsep Biokimia darah	10.1. Susunan dan fungsi darah	10.1.1. Memahami dan menjelaskan susunan darah 10.1.2. Memahami dan menjelaskan sifat- sifat darah 10.1.3. Memahami dan menjelaskan

		fungsi darah secara umum
	10.2. Protein plasma	10.2.1. Memahami dan menjelaskan sumber protein plasma 10.2.2. Memahami dan menjelaskan fungsi protein plasma 10.2.3. Memahami dan menjelaskan cara pemisahan protein plasma 10.2.4. Memahami dan menjelaskan kadar protein plasma dalam keadaan normal dan beberapa keadaan patologis
	10.3. Pembekuan darah	10.3.1. Memahami dan menjelaskan proses pembekuan darah dan faktor yang berperan 10.3.2. Memahami dan menjelaskan cara- cara pengaktifan faktor-faktor pembekuan darah
	10.4. Hemoglobin	10.4.1. Memahami dan menjelaskan fungsi Hb sebagai alat transpor oksigen 10.4.2. Memahami dan menjelaskan perbedaan struktur molekul Hb A, Hb F dan beberapa Hb abnormal 10.4.3. Memahami dan menjelaskan biosintesis hemoglobin 10.4.4. Memahami dan menjelaskan katabolisme hemoglobin
	10.5. Porfirin	10.5.1. Mengenal struktur porfirin 10.5.2. Memahami dan menjelaskan biosintesis porfirin 10.5.3. Mengenal penyakit-penyakit akibat gangguan biosintesis porfirin.
11. Memahami Kelainan Hematopoetik	11.1. Memahami dan menjelaskan kelainan sel darah putih yang bukan neoplasma	11.1.1. Memahami dan menjelaskan imflamasi :Lymfadenitis akut non spesifik , Lymadenitis kronik non spesifik 11.1.2. Lymadenitis kronik spesifik (TBC)

12. Memahami dan menjelaskan konsep dasar patologi klinik pada sistem Hematologi dan Limfatik	12.1. Memahami pendekatan diagnostik secara laboratorik untuk penyakit pada sistim hematologi dan hemostasis	12.1.1. Menjelaskan jenis-jenis pemeriksaan darah lengkap. 12.1.2. Mampu menginterpretasikan hasil pemeriksaan laboratorium darah lengkap dan morfologi darah tepi untuk diagnosis banding anemia (anemia defisiensi besi, anemia hemolitik, thalasemia, anemia makrositik, anemia penyakit kronik dll). 12.1.3. Mampu menjelaskan diagnosis dan diagnosis banding kelainan bentuk dan jumlah pada eritrosit, Leukosit dan trombosit 12.1.4. Mampu menjelaskan pemeriksaan hemostasis dasar (PT, APTT, TT, fibrinogen). 12.1.5. Mampu menjelaskan pemeriksaan hemostasis pada penyakit defisiensii faktor pembekuan dan

		gangguan perdarahan lain (VWD, hemofilia) 12.1.6. Mendiskusikan hasil laboratorium pada DIC. 12.1.7. Mampu mendiskusikan pemeriksaan hemostasis untuk monitoring pemakaian antikoagulan.
	12.2. Memahami pendekatan diagnosis secara laboratorik untuk pemeriksaan keganasan darah	12.2.1. Menyebutkan klasifikasi leukemia akut (WHO, FAB) 12.2.2. Mampu mendiskusikan pemeriksaan laboratorium untuk diagnosis dan monitoring pada leukemia akut (myelositik dan limfositik) 12.2.3. Mampu mendiskusikan pemeriksaan laboratorium untuk diagnosis dan monitoring pada leukemia kronis (myelositik, limfositik, MDS, dan MPD).
	12.3. Memahami dan menjelaskan pemeriksaan laboratorium pada transfusi komponen darah transfusi dan penggunaannya	12.3.1. Mampu mengetahui cara pemeriksaan golongan darah, Rhesus, dan *cross match*. 12.3.2. Mampu mengetahui jenis-jenis komponen darah untuk keperluan transfusi. 12.3.3. Mampu mengetahui pra analitik transfusi darah (skrining darah transfusi). 12.3.4. Mampu mengetahui jenis-jenis reaksi transfusi dan pemantauan reaksi transfusi.
13. Memahami parasit penyebab filariasis limfatik	13.1. Memahami parasit penyebab Wukereriasis (*Wuchereria bancrofti*)	*13.1.1.* Menerangkan distribusi geografis cacing *W. bancrofti* *13.1.2.* Menjelaskan morfologi *cacing W. bancrofti* 13.1.3. Menjelaskan siklus hidup cacing *W. bancrofti* 13.1.4. Menjelaskan pathogenesis wukereriasis 13.1.5. Menjelaskan manifestasi klinis wukereriasis bankrofti 13.1.6. Menjelaskan cara diagnosis wukereriasis bankrofti 13.1.7. Menjelaskan pengobatan dan pencegahan wukereriasis bankrofti

	13.2. Memahami parasit penyebab filariasis brugia (*Brugia malayi* & *Brugia timori*)	*13.2.1.* Menerangkan distribusi geografis cacing *B. malayi & B. timori* *13.2.2.* Menjelaskan morfologi *cacing B. malayi & B. timori* *13.2.3.* Menjelaskan siklus hidup cacing *B. malayi & B. timori* 13.2.4. Menjelaskan pathogenesis

		filariasis brugia 13.2.5. Menjelaskan manifestasi klinis filariasis brugia 13.2.6. Menjelaskan cara diagnosis filariasis brugia 13.2.7. Menjelaskan pengobatan dan pencegahan filariasis brugia
14. Memahami parasit penyebab filariasis non limfatik	14.1. Memahami parasit penyebab loaiasis (*Loa-loa*)	*14.1.1.* Menerangkan distribusi geografis cacing *Loa-loa* *14.1.2.* Menjelaskan morfologi *cacing Loa- loa* 14.1.3. Menjelaskan siklus hidup cacing *Loa-loa* 14.1.4. Memahami dan menjelaskan pathogenesis loaiasis 14.1.5. Menjelaskan manifestasi klinis loaiasis 14.1.6. Menerangkan cara diagnosis loaiasis 14.1.7. Menjelaskan pengobatan dan pencegahan loaiasis
	14.2. Memahami parasit penyebab onkoserkosis (*Onchocerca volvulus*)	*14.2.1.* Menjelaskan distribusi geografis cacing *Onchocerca volvulus* *14.2.2.* Menerangkan morfologi *cacing Onchocerca volvulus* 14.2.3. Menjelaskan siklus hidup cacing *Onchocerca volvulus* 14.2.4. Menjelaskan pathogenesis onkoserkosis 14.2.5. Menjelaskan manifestasi klinis onkoserkosis 14.2.6. Menjelaskan cara diagnosis onkoserkosis 14.2.7. Menjelaskan pengobatan dan pencegahan onkoserkosis

15. Menjelaskan epidemiologi filariasis limfatik dan non limfatik	15.1. Memahami epidemiologi filariasis limfatik	15.1.1. Mengetahui nama-nama penyakit filariasis limfatik 15.1.2. Mengetahui distribusi geografik penyakit filariasis limfatik (dunia dan Indonesia) 15.1.3. Mengetahui spesies penyebab penyakit filariasis limfatik (dunia dan Indonesia) 15.1.4. Memerinci daur hidup dari masing- masing spesies penyebab penyakit filariasis limfatik, termasuk perbedaannya 15.1.5. Menentukan suatu daerah endemis filariasis atau tidak 15.1.6. Menjelaskan hospes dan hospes reservoar yang berperan pada penyakit filariasis limfatik 15.1.7. Mengetahui vektor yang berperan pada penyakit filariasis limfatik 15.1.8. Menjelaskan bionomik vektor yang berperan pada penyakit filariasis

		limfatik 15.1.9. Menjelaskan faktor lingkungan yang berperan pada penyakit filariasis limfatik 15.1.10. Menjelaskan pengobatan filariasis berkaitan daerah endemis filariasis limfatik
	15.2. Memahami epidemiologi filariasis non limfatik	15.2.1. Menjelaskan nama-nama penyakit dan penyebab filariasis non limfatik 15.2.2. Menjelaskan distribusi geografik penyakit filariasis non limfatik 15.2.3. Menjelaskan spesies penyebab penyakit filariasis non limfatik 15.2.4. Menjelaskan vektor yang berperan pada penyakit filariasis non limfatik 15.2.5. Menjelaskan morfologi vektor yang berperan pada penyakit filariasis non limfatik
16. Memahami parasit trematoda darah	16.1. Memahami parasit trematoda darah penyebab penyakit skistosomiasis	16.1.1. Menjelaskan distribusi geografis cacing *Schistosoma japonicum* & *S. mansoni* *16.1.2.* Menjelaskan morfologi *cacing Schistosoma japonicum & S. mansoni* *16.1.3.* Menjelaskan siklus hidup cacing *Schistosoma japonicum & S. mansoni* 16.1.4. Menjelaskan pathogenesis skistosomiasis japonica *&* skistosomiasis usus 16.1.5. Menjelaskan manifestasi klinis skistosomiasis japonica & skistosomiasis usus 16.1.6. Menjelaskan cara diagnosis skistosomiasis japonica & skistosomiasis usus 16.1.7. Menjelaskan pengobatan dan pencegahan skistosomiasis japonica & skistosomiasis usus

17. Memahami parasit trematoda darah penyebab keganasan	17.1. Memahami parasit trematoda darah penyebab keganasan di vesica urinaria (*Schistosoma haematobium*)	*17.1.1.* Menjelaskan distribusi geografis cacing *Schistosoma haematobium* *17.1.2.* Menjelaskan morfologi *cacing Schistosoma haematobium* *17.1.3.* Menjelaskan dan menjelaskan siklus hidup cacing *Schistosoma haematobium* 17.1.4. Menjelaskan dan menjelaskan pathogenesis skistosomiasis haematobium dan keganasan vesica urinaria 17.1.5. Menjelaskan manifestasi klinis skistosomiasis haematobium dan keganasan vesica urinaria 17.1.6. Menjelaskan cara diagnosis *skistosomiasis haematobium* dan keganasan vesica urinaria

		17.1.7. Menjelaskan pengobatan dan pencegahan *skistosomiasis haematobium* dan keganasan vesica urinaria
18. Memahami dan menjelaskan diagnosis dan tatalaksana anemia, leukimia dan kelainan perdarahan	18.1. Memahami dan menjelaskan jenis- jenis obat anemia	18.1.1. Memahami farmakologi obat anemia defisiensi besi 18.1.2. Memahami farmakologi obat anemia defisiensi vitamin B_{12} 18.1.3. Memahami farmakologi obat anemia defisiensi asam folat 18.1.4. Memahami farmakologi obat anemia defisiensi obat lain
	18.2. Memahami dan menjelaskan jenis-jenis obat leukemia	18.2.1. Mahasiswa mampu menjelaskan farmakologi obat obat leukemia
	18.3. Memahami dan menjelaskan jenis- jenis obat-obat kelainan perdarahan	18.3.1. Memahami dan menjelaskan jenis- jenis obat untuk pencegahan dan pengobata tromboemboli dan untuk mengatasi perdarahan
19. Memahami dan menjelaskan kelainan hematopoetik dan limfatik pada pasien dewasa	19.1. Memahami dan menjelaskan kelainan eritrosit, leukosit dan trombosit pada pasien dewasa	19.1.1. Memahami dan menjelaskan kelainan yang terkait dengan eritrosit pada pasien dewasa 19.1.2. Memahami dan menjelaskan kelainan leukosit secara klinis pada pasien dewasa 19.1.3. Memahami dan menjelaskan kelainan trombosit secara klinis pada pasien dewasa
	19.2. Memahami dan menjelaskan diagnosis dan tatalaksana anemia, kelainan koagulasi dan fibrinolisis dan limfoma pasa pasien dewasa	19.2.1. Memahami dan menjelaskan diagnosis dan tatalaksana anemia pada orang dewasa 19.2.2. Memahami dan menjelaskan diagnosis dan tatalaksana kelainan koagulasi dan fibrinolisis pada orang dewasa 19.2.3. Memahami Limfoma Non Hodgkin dan Hodgkin secara klinis pada pasien dewasa

20. Memahami dan menjelaskan kelainan hematopoetik dan limfatik pada anak	20.1. Penatalaksanaan anemia dan leukemia pada anak 20.2. Penatalaksanaan gangguan hemostasis pada anak 20.3. Aplikasi transfusi darah pada anak	20.1.1. Manifestasi klinis 20.1.2. Diagnosis 20.1.3. Tatalaksana penyakit 20.1.4. Tatalaksana komplikasi penyakit 20.1.5. Prognosis

21. Memahami dan menjelaskan peran transfusi dan transplantasi secara Islam	21.1. Transfusi darah dan transplantasi organ ditinjau dari agama	21.1.1. Darah manusia sebagai makanan/obat, transfusi darah 21.1.2. Transplantasi organ, jual beli organ

RINCIAN RENCANA KEGIATAN

Pert/ Mggke	Capaian Pembelajaran (Sub-CPMK)	Indikator	Materi	Kegiatan pembelajaran (Metode)	Alokasi waktu	Sumber dan Media/alat	Penilaian/ Tugas
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
	Mengetahui pengertian dan aliran lymph	• Menjelaskan pengertian lymph ▪ Menjelaskan komposisi kandungan lymph ▪ Menjelaskan aliran lymph	Anatomi Pembuluh Lymph	Ceramah, tanya jawab Praktikum : 10' Kuis, 20' Pengantar Praktikum: 30' belajar dengan preparat dan atlas sendiri, 30' Tanya jawab dengan dosen	Kuliah: 2 x 50' Praktikum: 1 x 150' dr. Yenni Zulhamidah, MSc	Buku referensi TM : Power point, Laptop, Projektor LCD P : Cadaver dan Preparat	Ujian Tulis Ujian Praktikum
	Mengetahui pengertian, letak dan struktur pembuluh lymph	• Menjelaskan pengertian pembuluh lymph • Menjelaskan letak pembuluh- pembuluh lymph • Menjelaskan struktur pembuluh lymph	Anatomi Pembuluh Lymph	• Presentasi dosen, • Presentasi mahasiswa (individu, sampel acak) • Tanya jawab,			
	Mengetahui pengertian, letak dan struktur nodus lymphaticus	• Menjelaskan pengertian nodus lymphaticus • Menjelaskan letak nodi lymphatici • Menjelaskan struktur nodus lymphaticus	Anatomi nodus lymphaticus	Presentasi dosen, tanya jawab, diskusi			
	Mengetahui klasifikasi, letak, struktur, vascularisasi dan inervasi Tonsil	• Menjelaskan klasifikasi tonsil • Menjelaskan pengertian tonsilla palatina, tonsilla lingualis dan tonsilla pharyngea • Menjelaskan letak, tonsilla palatina, tonsilla lingualis dan tonsilla pharyngea • Menjelaskan struktur, tonsilla palatina, tonsilla lingualis dan tonsilla pharyngea • Menjelaskan vascularisasi dan inervasi, tonsilla palatina, tonsilla lingualis dan tonsilla pharyngea	Anatomi vascularisasi dan inervasi Tonsil	Diskusi kelas/kelompok, Presentasi dosen			
	Mengetahui letak, struktur, vascularisasi dan inervasi Thymus	• Menjelaskan pengertian thymus • Menjelaskan letak, thymus • Menjelaskan struktur thymus • Menjelaskan vascularisasi dan inervasi, thymus	Anatomi vascularisasi dan inervasi Thymus	Presentasi dosen, tanya jawab, diskusi			
	Mengetahui letak, struktur, vascularisasi dan inervasi Lien	• Menjelaskan pengertian lien • Menjelaskan letak lien • Menjelaskan struktur lien • Menjelaskan vascularisasi dan inervasi lien	Anatomi vascularisasi dan inervasi Lien	Presentasi dosen, tanya jawab, diskusi			
	Memahami histologi darah	• Menjelaskan nomenklatur dan susunan mikroskopis	Histologi darah	Kuliah	TM: Kuliah: 1x 50' (dr. Aan	Buku referensi Power point, Laptop,	Ujian Tulis

		eritrosit • Menjelaskan nomenklatur dan susunan mikroskopis jenis-jenis leukosit bergranula spesifik dan leukosit tidak bergranula spesifik • Menjelaskan nomenklatur dan susunan mikroskopis keping darah			Royhan MSc Kenconoviyati, S.Si. M. Biomed)	Projektor LCD -	
	Memahami	• Menjelaskan morfologi sel pada	Hematopoiesis	Kuliah	TM:	Buku referensi	Ujian Tulis

	hematopoiesis	hematopoiesis pada sel progenitor myeloid stem cell pada erythropoiesis, granulopoiesis dan thrombopoiesis • Menjelaskan morfologi sel pada limfopoiesis pada sel progenitor lymphoid stem cell • Menetapkan dengan mikroskop cahaya: - Eritrosit - Eosinofil - Basofil - Limfosit - Monosit - Trombosit		Praktikum (gabungan dengan bagian PK)	Kuliah: 1x 50' Praktikum : 1x150'	Power point, Laptop, Projektor LCD -	Ujian Praktikum
	Memahami histologi organ limfoid primer dan sekunder	• Menjelaskan susunan mikroskopis organ limfoid primer : thymus • Menjelaskan susunan mikroskopis organ limfoid sekunder : lien, tonsila, limfonodus • Menjelaskan susunan mikroskopis dan lokasi MALT (mucous associated lymphoid tissue) • Menjelaskan dan mengidentifikasi sel-sel darah yang berperan dalam sistem imun	Histologi Organ limfoid	kuliah	TM: Kuliah: 1x 50' (dr. Aan Royhan MSc Kenconoviyati, S.Si. M. Biomed)	Buku referensi, Power point, Laptop, Projektor LCD -	
	Memahami histologi kapiler limf, pembuluh limf sedang dan besar	• Menjelaskan susunan mikroskopis kapiler limf, pembuluh limf sedang dan besar • Menjelaskan perbedaan susunan mikroskopis pembuluh limf dengan pembuluh darah arteri dan vena • Menetapkan dengan mikroskop cahaya : - Organ limfoid primer : thymus - Organ limfoid sekunder : lien, limfonodus - MALT : tonsila, plaque peyeri - Sel-sel darah yang berperan dalam sistem imun : limfosit, makrofag, sel plasma, sel retikulum - Kapiler limf, pembuluh limf sedang dan besar	Histologi pembuluh limfe	kuliah praktikum	Kuliah: 1x 50' Praktikum: 1x150'	Buku referensi, Power point, Laptop, Projektor LCD -	Ujian Tulis Ujian Praktikum
	Mengetahui kelainan sel darah putih yang bukan neoplasia	• Mendefinisikan dan memahami inflamasi limfadenitis akut non spesifik, limfadenitis kronik non spesifik, dan limfadenitis kronik spesifik (TBC) • Menjelaskan patogenesis morfologi	Sistem hematopoetik dan limfoid	Kuliah Praktikum	Kuliah: 1x50' Praktikum: 1x150' (dr. Al Ichsan, Sp.PA)	Buku referensi, Power point, Laptop, Projektor LCD Jurnal, Laboratorium Patologi	Ujian Tulis, Ujian Praktikum

		• Menjelaskan gambaran patologi anatomi				Anatomi	
	Memahami neoplasia sel darah putih	• Mampu menjelaskan patogenesis morfologi kelainan ○ Limfoma non Hodgkin ○ Limfoma Hodgkin	Sistem hematopoetik dan limfoid	Kuliah Praktikum	Kuliah: 1x50' Praktikum: 1x150'	Buku referensi, Power point, Laptop, Projektor LCD	Ujian Tulis, Ujian Praktikum

		○ Menjelaskan perbedaan non Hodgkin dan Hodgkin ○ Mendefinisikan, memahami limfadenopati				Jurnal, Laboratorium Patologi Anatomi	
	Mengetahui kelainan-kelainan pada spleen (Lien)	• Mengetahui, mendefinisikan, dan memahami splenomegali • Mengetahui dan memahami kelainan-kelainan pada spleen	Spleen (Lien)	Kuliah Praktikum	Kuliah: 1x50' Praktikum: 1x150'	Buku referensi, Power point, Laptop, Projektor LCD Jurnal, Laboratorium Patologi Anatomi	Ujian Tulis, Ujian Praktikum
	Mengetahui neoplasia thymus	• Mengetahui hiperplasia thymus • Mengetahui thymoma	Thymus	Kuliah Praktikum	Kuliah: 1x50' Praktikum: 1x150'	Buku referensi, Power point, Laptop, Projektor LCD Jurnal, Laboratorium Patologi Anatomi	Ujian Tulis, Ujian Praktikum
	Memahami fungsi respirasi, transportasi, nutrisi, ekskresi, kekebalan, dan pengaturannya Memahami plasma dan elemen seluler darah Memahami eritropoiesis, leukopoiesis dan regulasinya Memahami dan menjelaskan gangguan eritrosit	• Mengidentifikasi komponen darah yang berfungsi respirasi, transportasi, nutrisi, ekskresi, kekebalan • Mengidentifikasi komponen pengaturan fungsi darah • Mengidentifikasi fungsi plasma • Mengidentifikasi sel darah merah, sel darah putih dan trombosit • Menjelaskan hematopoiesis • Mengidentifikasi regulasi hematopoiesis • Menjelaskan eritropoiesis • Menjelaskan fungsi hemoglobin • Menjelaskan sintesis hemoglobin • Menjelaskan peran eritopoietin, Vitamin B12, faktor instrinsik • Menjelaskan stimulasi dan regulasi leukopoiesis • Menyebutkan jenis-jenis anemia • Menjelaskan masing-masing penyebab anemia Menjelaskan penyebab polisitemia	Fungsi darah Fungsi plasma dan elemen seluler darah	Kuliah Tugas baca	TM: K : 1 x 50' Dr. dr. Diniwati Mukhtar, MKes	Buku referensi, Power point, Laptop, Projektor LCD Jurnal,	Ujian Tulis, Tugas Baca
	Mahasiswa mampu menjelaskan fisiologi hemostasis	• Mampu menjelaskan proses Hemostasis dan fibrinolisis	Fisiologi hemostasis dan fibrinolisis	Kuliah	Kuliah: 1x50'	Buku referensi, Power point, Laptop, Projektor LCD Jurnal	Ujian Tulis
	Susunan dan fungsi darah	• Memahami dan menjelaskan susunan darah • Memahami dan menjelaskan sifat- sifat darah • Memahami dan menjelaskan	Dasar-dasar Biokimia darah	Kuliah dan Tugas Baca	Kuliah: 2x50' Dr. Yulia Suciati,	Buku referensi, Power point, Laptop,	Ujian Tulis

		fungsi darah secara umum			M.Biomed, PhD	Projektor LCD Jurnal	
	Protein plasma	• Memahami dan menjelaskan sumber protein plasma • Memahami dan menjelaskan fungsi protein plasma • Memahami dan menjelaskan cara pemisahan protein plasma • Memahami dan menjelaskan kadar protein plasma dalam keadaan normal dan beberapa keadaan patologis					
	Pembekuan darah	• Memahami dan menjelaskan proses pembekuan darah dan					

		faktor yang berperan • Memahami dan menjelaskan cara- cara pengaktifan faktor-faktor pembekuan darah					
	Hemoglobin	• Memahami dan menjelaskan fungsi Hb sebagai alat transpor oksigen • Memahami dan menjelaskan perbedaan struktur molekul Hb A, Hb F dan beberapa Hb abnormal • Memahami dan menjelaskan biosintesis hemoglobin • Memahami dan menjelaskan katabolisme hemoglobin		Kuliah	Kuliah: 2x50' Dr. Yulia Suciati, M.Biomed, PhD	Buku referensi, Power point, Laptop, Projektor LCD Jurnal	Ujian Tulis
	Porfirin	• Mengenal struktur porfirin • Memahami dan menjelaskan biosintesis porfirin • Mengenal penyakit-penyakit akibat gangguan biosintesis porfirin.					
	Memahami parasit penyebab Wukereriasis (*Wuchereria bancrofti*)	• Menerangkan distribusi geografis cacing *W. bancrofti* • Menjelaskan morfologi *cacing W. bancrofti* • Menjelaskan siklus hidup cacing *W. bancrofti* • Menjelaskan pathogenesis wukereriasis • Menjelaskan manifestasi klinis wukereriasis bankrofti • Menjelaskan cara diagnosis wukereriasis bankrofti • Menjelaskan pengobatan dan pencegahan wukereriasis bankrofti	*Wuchereria bancrofti*	Kuliah dan Praktikum	TM: K: 1x50' P:1x150' (Filariasis limfatik ditambah materi Trematoda darah) dr. Isna Indrawati, MSc	Sutanto I, Ismid IS, Sjarifuddin PK, Sungkar S (Ed) (2013): Parasitologi Kedokteran, FKUI Komputer LCD	Ujian Tulis Ujian Praktikum
	Memahami parasit penyeb ab filariasis brugia (*Brugia malayi & Brugia timori*)	• Menerangkan distribusi geografis cacing *B. malayi & B. timori* • Menjelaskan morfologi *cacing B. malayi & B. timori* • Menjelaskan siklus hidup cacing *B. malayi & B. timori* • Menjelaskan pathogenesis filariasis brugia • Menjelaskan manifestasi klinis filariasis brugia • Menjelaskan cara diagnosis filariasis brugia • Menjelaskan pengobatan dan pencegahan filariasis brugia	*Brugia malayi & Brugia timori*				
	Memahami parasit penyebab loaiasis (*Loa-loa*)	• Menerangkan distribusi geografis cacing *Loa-loa* • Menjelaskan morfologi *cacing Loa-loa* • Menjelaskan siklus	*Loa-loa*	Tugas mandiri (Tugas baca)	TM: K: 1x50' dr. Elita Donanti,	Sutanto I, Ismid IS, Sjarifuddin PK, Sungkar S (Ed)	Ujian Tulis

		hidup cacing *Loa-loa* • Memahami dan menjelaskan pathogenesis loaiasis • Menjelaskan manifestasi klinis loaiasis • Menerangkan cara diagnosis loaiasis • Menjelaskan pengobatan dan pencegahan loaiasis			M.Biomed	(2013): Parasitologi Kedokteran, FKUI KomputerLCD	
	Memahami parasit penyebab onkoserkosis	• Menjelaskan distribusi geografis cacing *Onchocerca volvulus* • Menerangkan morfologi *cacing Onchocerca volvulus*	*Onchocerca volvulus*	Tugas mandiri (Tugas baca)			

	(*Onchocerca volvulus*)	• Menjelaskan siklus hidup cacing *Onchocerca volvulus* • Menjelaskan pathogenesis onkoserkosis • Menjelaskan manifestasi klinis onkoserkosis • Menjelaskan cara diagnosis onkoserkosis • Menjelaskan pengobatan dan pencegahan onkoserkosis					
	Memahami epidemiologi filariasis limfatik	• Mengetahui nama-nama penyakit filariasis limfatik • Mengetahui distribusi geografik penyakit filariasis limfatik (dunia dan Indonesia) • Mengetahui spesies penyebab penyakit filariasis limfatik (dunia dan Indonesia) • Memerinci daur hidup dari masing-masing spesies penyebab penyakit filariasis limfatik, termasuk perbedaannya • Menentukan suatu daerah endemis filariasis atau tidak • Menjelaskan hospes dan hospes reservoar yang berperan pada penyakit filariasis limfatik • Mengetahui vektor yang berperan pada penyakit filariasis limfatik • Menjelaskan bionomik vektor yang berperan pada penyakit filariasis limfatik • Menjelaskan faktor lingkungan yang berperan pada penyakit filariasis limfatik • Menjelaskan pengobatan filariasis berkaitan daerah endemis filariasis limfatik	Filariasi Limfatik	Kuliah	TM: K: 1x50' dr. Rika Ferlianti, M.Biomed	Sutanto I, Ismid IS, Sjarifuddin PK, Sungkar S (Ed) (2013): Parasitologi Kedokteran, FKUI KomputerLCD	Ujian Tulis
	Memahami epidemiologi filariasis non limfatik	• Menjelaskan nama-nama penyakit dan penyebab filariasis non limfatik • Menjelaskan distribusi geografik penyakit filariasis non limfatik • Menjelaskan spesies penyebab penyakit filariasis non limfatik	Filariasis non limfatik	Kuliah	TM: K: 1x50' dr. Rika Ferlianti, M.Biomed	Sutanto I, Ismid IS, Sjarifuddin PK, Sungkar S (Ed) (2013): Parasitologi Kedokteran, FKUI	Ujian Tulis

		• Menjelaskan vektor yang berperan pada penyakit filariasis non limfatik • Menjelaskan morfologi vektor yang berperan pada penyakit filariasis non limfatik				KomputerLCD	
	Memahami parasit trematoda darah penyebab penyakit skistosomiasis	• Menjelaskan distribusi geografis cacing *Schistosoma japonicum & S. mansoni* • Menjelaskan morfologi *cacing Schistosoma japonicum & S. mansoni* • Menjelaskan siklus hidup cacing *Schistosoma japonicum & S. mansoni* • Menjelaskan pathogenesis skistosomiasis japonica *&* skistosomiasis usus • Menjelaskan manifestasi klinis	Skistosomiasis	Kuliah	TM: K: 1x50' P:pelaksanaan digabung dengan prakt. Filariasis limfatik dr. Isna Indrawati MSc	Sutanto I, Ismid IS, Sjarifuddin PK, Sungkar S (Ed) (2013): Parasitologi Kedokteran, FKUI KomputerLCD	Ujian Tulis Ujian Praktikum

		skistosomiasis japonica & skistosomiasis usus • Menjelaskan cara diagnosis skistosomiasis japonica & skistosomiasis usus • Menjelaskan pengobatan dan pencegahan • skistosomiasis japonica & skistosomiasis usus					
	Memahami parasit trematoda darah penyebab keganasan di vesica urinaria (*Schistosoma haematobium*)	• Menjelaskan distribusi geografis cacing • *Schistosoma haematobium* • Menjelaskan morfologi *cacing Schistosoma haematobium* • Menjelaskan dan menjelaskan siklus hidup cacing *Schistosoma haematobium* • Menjelaskan dan menjelaskan pathogenesis skistosomiasis haematobium dan keganasan vesica urinaria • Menjelaskan manifestasi klinis skistosomiasis haematobium dan keganasan vesica urinaria • Menjelaskan cara diagnosis *skistosomiasis haematobium* dan keganasan vesica urinaria • Menjelaskan pengobatan dan pencegahan *skistosomiasis haematobium* dan keganasan vesica urinaria	*Schistosoma haematobium*				
	Memahami dan menjelaskan kelainan eritrosit, leukosit dan trombosit pada pasien dewasa	• Memahami dan menjelaskan kelainan yang terkait dengan eritrosit pada pasien dewasa	kelainan yang terkait dengan eritrosit	Kuliah Tutorial	Kuliah : 1x50' Tutorial : 1x100' DR. dr. Faizal Drissa Hasibuan, SpPD, KHOM	Buku ajar Jurnal	Ujian Tulis Kuis dan wrap up
		• Memahami dan menjelaskan kelainan leukosit secara klinis pada pasien dewasa	kelainan leukosit	Kuliah	Kuliah : 1x50' DR. dr. Faizal Drissa Hasibuan, SpPD, KHOM	Buku ajar Jurnal	Ujian Tulis
		• Memahami dan menjelaskan kelainan trombosit secara klinis pada pasien dewasa	kelainan trombosit	Kuliah Tutorial	Kuliah : 1x50' Tutorial : 1x100'	Buku ajar Jurnal	Ujian Tulis Kuis dan wrap up

					DR. dr. Faizal Drissa Hasibuan, SpPD, KHOM		
	Memahami dan menjelaskan diagnosis dan tatalaksana anemia, kelainan koagulasi dan fibrinolisis dan limfoma pasa pasien dewasa	• Memahami dan menjelaskan diagnosis dan tatalaksana anemia pada orang dewasa	diagnosis dan tatalaksana anemia	Kuliah Tugas Baca	Kuliah : 1x50' DR. dr. Faizal Drissa Hasibuan, SpPD, KHOM	Buku ajar Jurnal	Ujian Tulis Kuis
		• Memahami dan menjelaskan diagnosis dan tatalaksana kelainan koagulasi dan fibrinolisis pada orang dewasa	diagnosis dan tatalaksana kelainan koagulasi dan fibrinolisis	Kuliah	Kuliah : 1x50' DR. dr. Faizal Drissa Hasibuan, SpPD, KHOM	Buku ajar Jurnal	Ujian Tulis
		• Memahami Limfoma Non Hodgkin dan Hodgkin secara klinis pada pasien dewasa	Limfoma Non Hodgkin dan Hodgkin	Kuliah	Kuliah : 1x50' DR. dr. Faizal Drissa Hasibuan, SpPD, KHOM	Buku ajar Jurnal	Ujian Tulis

	Penatalaksanaan anemia dan leukemia pada anak	• Manifestasi klinis • Diagnosis • Tatalaksana penyakit • Tatalaksana komplikasi penyakit • Prognosis	Anemia dan Leukimia pada anak	Kuliah	Kuliah : 2x50' dr. Elsye, SpA	Buku ajar Jurnal	Ujian Tulis
	Penatalaksanaan gangguan hemostasis pada anak	• Manifestasi klinis • Diagnosis • Tatalaksana penyakit • Tatalaksana komplikasi penyakit • Prognosis	Gangguan hemostasis pada anak	Kuliah	Kuliah : 2x50' dr. Elsye, SpA	Buku ajar Jurnal	Ujian Tulis
	Aplikasi transfusi darah pada anak			Kuliah	Kuliah : 2x50' dr. Elsye, SpA	Buku ajar Jurnal	Ujian Tulis
	Memahami dan menjelaskan pendekatan diagnostik secara laboratorik untuk penyakit pada sistim hematologi dan hemostasis	• Menjelaskan jenis-jenis pemeriksaan darah rutin, lengkap. • Mampu menjelaskan kelainan bentuk dan jumlah pada eritrosit, Leukosit dan trombosit • Mampu menjelskan, menginterpretasikan, hasil pemeriksaan laboratorium darah lengkap dan morfologi darah tepi untuk diagnosis banding anemia (anemia defisiensi besi, anemia hemolitik, thalasemia, anemia makrositik, anemia penyakit kronik dll). • Mampu menjelaskan jenis dan interpretasi pemeriksaan hemostasis dasar (PT, APTT, TT, fibrinogen), Fibrinolisis • Mampu menjelaskan pemeriksaan hemostasis pada penyakit defisiensii faktor pembekuan dan gangguan perdarahan lain (VWD, hemofilia) • Mampu menjelaskan hasil laboratorium pada DIC. • Mampu menjelaskan pemeriksaan hemostasis untuk monitoring pemakaian antikoagulan	pendekatan diagnostik secara laboratorik untuk penyakit pada sistim hematologi dan hemostasis	Kuliah Praktikum Tutorial	Kuliah : 11x50' Praktikum: 6x150' Tutorial: 3x100' (DR. dr. Anggraini Iriani, SpPK dr. Farida Amin, SpPK dr. Bambang Purwantoro, MHKes dr. Endah Purnamasari, SpPK dr. Syukrini Bahri, SpPK)	Buku referensi, Power point, Laptop, Projektor LCD Jurnal, Laboratorium Diskusi kelompok	Ujian Tulis, Ujian Praktikum, Kuis dan wrap up
	Memahami pendekatan diagnosis secara laboratorik untuk pemeriksaan keganasan darah	• Menyebutkan klasifikasi Leukemia akut (WHO) • Menyebutkan klasifikasi Leukemia kronik (WHO) • menjelaskan pemeriksaan laboratorium untuk diagnosis dan monitoring pada leukemia akut (myelositik dan limfositik) • 4. menjelaskan pemeriksaan laboratorium untuk diagnosis dan monitoring pada leukemia kronis (myelositik, limfositik, MDS, dan MPD).	pendekatan diagnosis secara laboratorik untuk pemeriksaan keganasan darah	Kuliah Praktikum	Kuliah : 2x50' Praktikum: 1x150'	Buku referensi, Power point, Laptop, Projektor LCD Jurnal, Laboratorium Diskusi kelompok	Ujian Tulis Ujian Praktikum Kuis
	Memahami dan menjelaskan pemeriksaan laboratorium pada transfusi komponen darah transfusi dan penggunaannya	• Mampu mengetahui cara pemeriksaan golongan darah, Rhesus, dan *cross match*. • Mampu mengetahui jenis-jenis komponen darah untuk keperluan transfusi. • Mampu mengetahui pra analitik transfusi darah (skrining darah transfusi). • Mampu mengetahui jenis ,pemantauan dan pelaporan reaksi	pemeriksaan laboratorium pada transfusi komponen darah transfusi dan penggunaanny a	Kuliah Tutorial	Kuliah : 1x50' Tutorial : 1x100'	Buku referensi, Power point, Laptop, Projektor LCD Jurnal, buku ajar Diskusi kelompok	Ujian Tulis, ujian praktikum, Kuis dan wrap up

		transfusi.					
	Transfusi darah dan transplantasi organ ditinjau dari agama	• Darah manusia sebagai makanan/obat, transfusi darah • Transplantasi organ, jual beli organ	Transfusi dan transplantasi secara Islam	Kuliah	Kuliah : 2x50' (Drs. M. Arsyad, M.Ag)	Buku referensi, Power point, Laptop, Projektor LCD	Ujian Tulis

EVALUASI PEMBELAJARAN

FORMULA ASSESMEN BLOK (%)	
Nilai Ujian Teori	52,5
Nilai tugas	15
Nilai praktikum	12,5
Nilai kuis dan wrap up	20

	Rentang Nilai		Arti
Range	Angka	Huruf	
≥75	4.00	A	Lulus
72,50 – 74,99	3.75	A-	Lulus
70,00 – 72,49	3.50	AB	Lulus
67,50 - 69,99	3.25	B+	Lulus
65,00 – 67,49	3.00	B	Lulus
62,50 – 64,99	2.75	B-	Lulus
60,00 – 62,49	2.50	BC	Lulus
57,50 – 59,99	2.25	C+	Lulus
55,00 – 57,49	2.00	C	Lulus
52,50 – 54,99	1.75	C-	Tidak Lulus
50,00 – 52,49	1.50	CD	Tidak Lulus
47,50 – 49,99	1.25	D+	Tidak Lulus
45,00 – 47,49	1.00	D	Tidak Lulus
≤ 45	0.00	E	Tidak Lulus

PANDUAN TUGAS MAHASISWA

TUGAS 1. Sel – sel darah dan Hematopoietik

	UNIVERSITAS YARSI **FAKULTAS KEDOKTERAN** **PROGRAM STUDI KEDOKTERAN UMUM**				
MATA KULIAH	Histologi Blok Hematopoetik dan Limfatik				
KODE	KK1104002_18	SKS	6	Semester	4
DOSEN PENGAMPU	Kenconoviyati SSi.,M. Biomed				
BENTUK TUGAS					
Membaca bab Blood and Hematopoietic dari buku teks Hstologi seperti pada daftar bacaan					
JUDUL TUGAS					
Tugas 3. Sel – sel darah dan Hematopoietik					
SUB CAPAIAN PEMBELAJARAN MATA KULIAH					
Mahasiswa mampu menjelaskan dan membedakan sel-sel darah dan sel pada eritropoiesis, trombopoiesis, limfopoieis					
DISKRIPSI TUGAS					
Membaca bab darah dan hematopoietic pada text and atlas histologi lalu menjawab pertanyaan yang ada dilembar tugas paa saat feedback					
METODE PENGERJAAN TUGAS					
Membaca dan menjawab soal					
BENTUK DAN FORMAT LUARAN					
Kuis dan feedback					
INDIKATOR, KRETERIA DAN BOBOT PENILAIAN					
Penilaian kuis menggunakan kunci yang disediakan oleh Pengampu mata kuliah Histologi pada Blok Hematopoetik dan Limfatik. Bobot penilaian tugas baca 15%.					
JADWAL PELAKSANAAN					
• Membaca	Minggu 1 blok berjalan				
• Identifikasi hal yang belum dipahami	Di email ke kencono.viyati@yarsi.ac.id paling lambat 2 hari sebelum feedback				
• Kuis dan Feedback	Kelas A : 1x50’ Kelas B : 1x50’				
LAIN-LAIN					
Feedback dilaksanakan dikelas reguler					
DAFTAR RUJUKAN					
Mescher, Anthony L. : Junqueira’s Basic Histology Text and Atlas,13th edition, Mc GrawHill Eucation, international edition, 2013, pp. 234-261					

TUGAS 2. Pembekuan Darah

	UNIVERSITAS YARSI **FAKULTAS KEDOKTERAN** **PROGRAM STUDI KEDOKTERAN UMUM**				
MATA KULIAH	Biokimia Blok Hematopoetik dan Limfatik				
KODE	KK1104002_18	SKS	6	Semester	4
DOSEN PENGAMPU	dr. Yulia Suciati, M.Biomed, PhD				
BENTUK TUGAS					
Membaca satu bab dari buku teks Hematologi seperti pada daftar bacaan					
JUDUL TUGAS					
Tugas 1. **Pembekuan darah**					
SUB CAPAIAN PEMBELAJARAN MATA KULIAH					
Mahasiswa mampu menjelaskan dan membedakan prinsip serta konsep pembekuan darah					
DISKRIPSI TUGAS					
Membaca bab pada buku teks Hematologi yang ada pada daftar bacaan dan membuat pertanyaan dengan identifikasi hal-hal yang belum dipahami. Pertanyaan diemailkan ke alamat email yang tercantum dibawah					
METODE PENGERJAAN TUGAS					
Mencatat dan mempersiapkan bahan diskusi.					
BENTUK DAN FORMAT LUARAN					
Kuis dan feedback					
INDIKATOR, KRETERIA DAN BOBOT PENILAIAN					
Penilaian kuis menggunakan kunci yang disediakan oleh Pengampu mata kuliah Biokimia Blok Hematopoetik dan Limfatik. Bobot penilaian tugas baca 15%.					
JADWAL PELAKSANAAN					
• Membaca	1 minggu sebelum feedback Biokimia				
• Identifikasi hal yang belum dipahami	Di email ke yulia.suciati@yarsi.ac.id paling lambat 2 hari sebelum feedback Biokimia				
• Kuis dan Feedback	klas A : 1x50’ klas B : 1x50’				
LAIN-LAIN					
Feedback dilaksanakan dikelas reguler					
DAFTAR RUJUKAN					
jurnal terlampir					

TUGAS 3. Filariasis Non Limfatik

	UNIVERSITAS YARSI **FAKULTAS KEDOKTERAN** **PROGRAM STUDI KEDOKTERAN UMUM**				
MATA KULIAH	Parasitologi Blok Hematopoetik dan Limfatik				
KODE	KK1104002_18	SKS	6	Semester	4
DOSEN PENGAMPU	dr. Elita Donanti, M.Biomed				
BENTUK TUGAS					
Membaca materi Filariasis Non Limfatik dari buku teks Parasitic Diseases seperti pada daftar bacaan					
JUDUL TUGAS					
Tugas 1. Filariasis Non Limfatik					
SUB CAPAIAN PEMBELAJARAN MATA KULIAH					
Mahasiswa mampu menjelaskan 2 parasit penyebab filariasis non limfatik mulai dari morfologi, daur hidup, patogenesis dan manifestasi klinis, cara diagnosis serta pencegahannya					
DISKRIPSI TUGAS					
Membaca materi Filariasis Non Limfatik dari buku teks Parasitic Diseases seperti pada daftar bacaan dan membuat pertanyaan terkait materi yang belum dipahami. Pertanyaan dapat dikirimkan ke alamat email yang ada di bawah.					
METODE PENGERJAAN TUGAS					
Mencatat dan mempersiapkan bahan diskusi.					
BENTUK DAN FORMAT LUARAN					
Kuis dan feedback					
INDIKATOR, KRETERIA DAN BOBOT PENILAIAN					
Penilaian kuis menggunakan kunci yang disediakan oleh Pengampu mata kuliah Parasitologi Blok Hematopoetik dan Limfatik. Bobot penilaian tugas baca 15%.					
JADWAL PELAKSANAAN					
• Membaca	1 minggu sebelum feedback Parasitologi				
• Identifikasi hal yang belum dipahami	Di email ke elita.donanti@yarsi.ac.id paling lambat 2 hari sebelum feedback Parasitologi				
• Feedback	1 x 50 menit				
• Kuis	Diberikan melalui layar PJJ YARSI 2 hari sebelum pelaksanaan feedback Parasitologi				
LAIN-LAIN					
Feedback dilaksanakan di kelas reguler					
DAFTAR RUJUKAN					
jurnal terlampir					

TUGAS 4. HEMATOPOIESIS PADA USIA LANJUT

	UNIVERSITAS YARSI **FAKULTAS KEDOKTERAN** **PROGRAM STUDI KEDOKTERAN UMUM**				
MATA KULIAH	Fisiologi Blok Hematopoetik dan Limfatik				
KODE	KK1104002_18	SKS	6	Semester	4
DOSEN PENGAMPU	Dr. dr.Diniwati Mukhtar MKes				
BENTUK TUGAS					
Membaca satu bab dari buku teks fisiologi atau jurnal					
JUDUL TUGAS					
Tugas 4. Hematopoiesis pada usia lanjut					
SUB CAPAIAN PEMBELAJARAN MATA KULIAH					
Mahasiswa mampu menjelaskan prinsip hematopoiesis pada usia lanjut					
DISKRIPSI TUGAS					
Membaca bab pada buku teks fisiologi dan jurnal dan membuat pertanyaan dengan identifikasi hal-hal yang belum dipahami. Pertanyaan diemailkan ke alamat email yang tercantum dibawah					
METODE PENGERJAAN TUGAS					
Mencatat dan mempersiapkan bahan diskusi.					
BENTUK DAN FORMAT LUARAN					
Kuis dan feedback					
INDIKATOR, KRETERIA DAN BOBOT PENILAIAN					
Penilaian kuis menggunakan kunci yang disediakan oleh Pengampu mata kuliah Fisiologi pada Blok Hematopoetik dan Limfatik. Bobot penilaian tugas baca 15%.					
JADWAL PELAKSANAAN					
• Membaca	1 minggu sebelum feedback Fisiologi				
• Identifikasi hal yang belum dipahami	Di email ke diniwati.mukhtar@yarsi.ac.id paling lambat 2 hari sebelum feedback Fisiologi				
• Kuis dan Feedback	Kelas A : 1x50’ Kelas B : 1x50’				
LAIN-LAIN					
Feedback dilaksanakan dikelas reguler					
DAFTAR RUJUKAN					
Snoeck HW. Aging of the hematopoietic system. Curr Opin Hematol. 2013 Jul;20(4):355-61. doi: 10.1097/MOH.0b013e3283623c77. PMID: 23739721. (jurnal terlampir)					

TUGAS 5. Acute Myeloid Leukimia (AML)

	UNIVERSITAS YARSI **FAKULTAS KEDOKTERAN** **PROGRAM STUDI KEDOKTERAN UMUM**				
MATA KULIAH	Patologi Klinik Blok Hematopoetik dan Limfatik				
KODE	KK1104002_18	SKS	6	Semester	4
DOSEN PENGAMPU	DR. dr. Angraini Iriani, SpPK				
BENTUK TUGAS					
Membaca satu jurnal Patologi Klinik pada lampiran					
JUDUL TUGAS					
Tugas 6. Acute Myeloid Leukimia (AML)					
SUB CAPAIAN PEMBELAJARAN MATA KULIAH					
Mahasiswa mampu menjelaskan mengenai Acute Myeloid Leukimia (AML)					
DISKRIPSI TUGAS					
Membaca jurnal Patologi Anatomi yang ada pada lampiram dan membuat pertanyaan mengenai hal-hal yang belum dipahami. Pertanyaan diemailkan ke alamat email yang tercantum dibawah					
METODE PENGERJAAN TUGAS					
Mencatat dan mempersiapkan bahan diskusi.					
BENTUK DAN FORMAT LUARAN					
Kuis dan feedback					
INDIKATOR, KRETERIA DAN BOBOT PENILAIAN					
Penilaian kuis menggunakan kunci yang disediakan oleh Pengampu mata kuliah Patologi Klinik pada Blok Hematopoetik dan Limfatik. Bobot penilaian tugas baca 15%.					
JADWAL PELAKSANAAN					
• Membaca	1 Minggu sebelum Feedback Patologi Klinik				
• Identifikasi hal yang belum dipahami	Di email ke anggraini.iriani@yarsi.ac.id paling lambat 2 hari sebelum feedback patologi klinik				
• Kuis dan Feedback	Kelas A : 1x50’ Kelas B : 1x50’				
LAIN-LAIN					
Feedback dilaksanakan dikelas reguler					
DAFTAR RUJUKAN					
Jurnal terlampir					

TUGAS 6. Obat Leukemia

	UNIVERSITAS YARSI **FAKULTAS KEDOKTERAN** **PROGRAM STUDI KEDOKTERAN UMUM**				
MATA KULIAH	Farmakologi Blok Hematopoetik dan Limfatik				
KODE	KK1104002_18	SKS	6	Semester	4
DOSEN PENGAMPU	Dr. Risdawati Djohan. M.Kes., Apt				
BENTUK TUGAS					
Membaca satu bab materi dari buku teks Farmakologi seperti pada daftar bacaan					
JUDUL TUGAS					
Tugas 2. Obat Leukemia					
SUB CAPAIAN PEMBELAJARAN MATA KULIAH					
Mahasiswa mampu memahami farmakologi obat antikanker yang diindikasikan untuk leukemia akut dan kronik					
DISKRIPSI TUGAS					
Membaca uraian obat untuk leukemia pada bab antikanker Canser chemotheraphy) buku teks farmakologi yang tercantum pada daftar bacaan dan mengidentifikasi hal-hal yang belum dipahami kemudian menyusun pertanyaan. Pertanyaan dikirimkan ke alamat email yang tercantum dibawah.					
METODE PENGERJAAN TUGAS					
Mencatat dan mempersiapkan bahan diskusi.					
BENTUK DAN FORMAT LUARAN					
Kuis dan feedback					
INDIKATOR, KRETERIA DAN BOBOT PENILAIAN					
Penilaian kuis menggunakan kunci yang disediakan oleh Pengampu mata kuliah Farmakologi pada Blok Hematopoetik dan Limfatik. Bobot penilaian tugas baca 15%.					
JADWAL PELAKSANAAN					
• Membaca	1 minggu sebelum feedback Farmakologi				
• Identifikasi hal yang belum dipahami	Di email ke risdawati@yarsi.ac.id paling lambat 2 hari sebelum feedback farmakologi				
• Kuis dan Feedback	Kelas A : 1x50' Kelas B : 1x50'				
LAIN-LAIN					
Feedback dilaksanakan dikelas reguler					
DAFTAR RUJUKAN					
EdwardChu and Sartorelli A.C. 2012. **Chapter 54:** Cancer Chemotherapy. Katzung's Basic & Clinical Pharmacology. 12th edition. McGraw-Hill. USA. p. 969 – 976 Chabner B.A. 2011. **Chapter 60**: General Principles of Cancer Chemotheraphy *Goodman & Gilman's* The Pharmacological Basis of Therapeutics. 12th edition. McGraw-Hill. USA. p.1667-1675 Chabner B.A., Bertino J., Cleary J., Ortiz T.,Lane A., Supko J.G., and Ryan D. 2011. **Chapter 61**: Cytotoxic Agents. *Goodman & Gilman's* The Pharmacological Basis of Therapeutics. 12th edition. McGraw-Hill. USA. p.1678-1731 Chabner B.A., Barnes J., Neal J., Plson E., Mujagic H., Sequist L., Wilson W., Longo DL., Mitsiades C., and Richardson P. 2011. **Chapter 62**: Targeted Therapies: Tyrosin Kinase Inhibitor *Goodman & Gilman's* The Pharmacological Basis of Therapeutics. 12th edition. McGraw-Hill. USA. p.1732-1754 Moy B., Lee R.J., and Smith M. 2011. **Chapter 63**: Natural Products in Cancer Chemotheraphy: Hormones and Related Agents. *Goodman & Gilman's* The Pharmacological Basis of Therapeutics. 12th edition. McGraw-Hill. USA. p.1756-1770 Nafrialdi dan Gan S. 2016. **Bab 47:** Antikanker. Farmakologi dan Terapi. Edisi 6. Penerbit: Badan Penerbit FKUI. Jakarta. p737-762					

TUGAS 7. Reaktif proliferasi kelanjar Getah Bening

	UNIVERSITAS YARSI **FAKULTAS KEDOKTERAN** **PROGRAM STUDI KEDOKTERAN UMUM**				
MATA KULIAH	Patologi Anatomi Blok Hematopoetik dan Limfatik				
KODE	KK1104002_18	SKS	6	Semester	4
DOSEN PENGAMPU	dr. Al Ichsan, Sp. PA				
BENTUK TUGAS					
Membaca satu bab dari buku teks Patologi Anatomi seperti pada daftar bacaan					
JUDUL TUGAS					
Tugas 5. Reaktif proliferasi kelanjar Getah Bening					
SUB CAPAIAN PEMBELAJARAN MATA KULIAH					
Mahasiswa mampu menjelaskan mengenai Reaktif proliferasi kelenjar Getah bening					
DISKRIPSI TUGAS					
Membaca bab pada buku teks Patologi Anatomi yang ada pada daftar bacaan dan membuat pertanyaan mengenai hal-hal yang belum dipahami. Pertanyaan diemailkan ke alamat email yang tercantum dibawah					
METODE PENGERJAAN TUGAS					
Mencatat dan mempersiapkan bahan diskusi.					
BENTUK DAN FORMAT LUARAN					
Kuis dan feedback					
INDIKATOR, KRETERIA DAN BOBOT PENILAIAN					
Penilaian kuis menggunakan kunci yang disediakan oleh Pengampu mata kuliah Patologi Anotomi pada Blok Hematopoetik dan Limfatik. Bobot penilaian tugas baca 15%.					
JADWAL PELAKSANAAN					
• Membaca	1 minggu sebelum Feedback Patologi Anatomi				
• Identifikasi hal yang belum dipahami	Di email ke al.ichsan@yarsi.ac.id paling lambat 2 hari sebelum feedback patologi anatomi				
• Kuis dan Feedback	Kelas A : 1x50’ Kelas B : 1x50’				
LAIN-LAIN					
Feedback dilaksanakan dikelas reguler					
DAFTAR RUJUKAN					
Robbins SL, Kumar V , 2015.Diseases of White Blood Cells, Lymph Nodes, Spleen , and Thymus. Dalam Patologic Basis of Disease, hal 583 –586					

TUGAS 8. Pemilihan Produk Transfusi Darah

	UNIVERSITAS YARSI **FAKULTAS KEDOKTERAN** **PROGRAM STUDI KEDOKTERAN UMUM**				
MATA KULIAH	Ilmu Penyakit Dalam Blok Hematopoetik dan Limfatik				
KODE	KK1104002_18	SKS	6	Semester	4
DOSEN PENGAMPU	Dr. Faizal Drissa Hasibuan, SpPD KHOM				
BENTUK TUGAS					
Membaca empat bab dari buku teks Hematologi seperti pada daftar bacaan					
JUDUL TUGAS					
Tugas 1. **Pemilihan Produk Transfusi Darah**					
SUB CAPAIAN PEMBELAJARAN MATA KULIAH					
Mahasiswa mampu menjelaskan dan membedakan prinsip serta konsep dalam pemilihan produk darah yang sesuai indikasi					
DISKRIPSI TUGAS					
Membaca bab pada buku teks Hematologi yang ada pada daftar bacaan dan membuat pertanyaan dengan identifikasi hal-hal yang belum dipahami. Pertanyaan diemailkan ke alamat email yang tercantum dibawah					
METODE PENGERJAAN TUGAS					
Mencatat dan mempersiapkan bahan diskusi.					
BENTUK DAN FORMAT LUARAN					
Kuis dan feedback					
INDIKATOR, KRETERIA DAN BOBOT PENILAIAN					
Penilaian kuis menggunakan kunci yang disediakan oleh Pengampu mata kuliah Ilmu Penyakit Dalam Blok Hematopoetik dan Limfatik. Bobot penilaian tugas baca 15%.					
JADWAL PELAKSANAAN					
• Membaca	1 minggu sebelum feedback IPD				
• Identifikasi hal yang belum dipahami	Di email ke faizal.drissa@yarsi.ac.id paling lambat 2 hari sebelum feedback IPD				
• Kuis dan Feedback	klas A : 1x50’ klas B : 1x50’				
LAIN-LAIN					
Feedback dilaksanakan dikelas reguler					
DAFTAR RUJUKAN					
Hillyer, Sillberstein, Ness, et al. 2007. **Chapter 18**: Packed Red Blood Cells and Related Products pp 250-256, **Chapter 19** : Fresh Frozen Plasma and Related Products pp 259-266, **Chapter 20** : Cryoprecipitate and Related Products pp 270-275, **Chapter 23** : Platelets and Related Products, pp 325-328. . Blood Banking and Transfusion Medicine: Basic Principles & Practice. 2nd Ed. Elsevier.Philadelphia. USA.					

SKENARIO 1

SERING PUSING DAN JALAN TERASA MELAYANG

Seorang perempuan berumur 45 tahun dengan keluhan sering pusing dan jalan terasa melayang, datang ke Poliklinik RS. Beliau juga memiliki riwayat Menorrhagia sejak 1 tahun terakhir. Tidak ada riwayat alergi obat dan makanan. Asupan makanan juga baik dan tidak vegetarian. Dari pemeriksaan fisik didapat conjunctiva pucat, palmar tangan pucat, mukosa bukal pucat. Paru, Jantung, Abdomen dalam batas normal. Dilanjutkan pemeriksaan penunjang darah rutin dengan hasil Hb 6,2 gr/dL, Ht 18,8 , Lekosit 5400 Trombosit 234.000 dan hasil morfologi darah tepi eritrosit didapat anemia mikrositik hipokromik dengan sel pensil.

SKENARIO 2

MIMISAN SULIT BERHENTI

Seorang laki-laki, umur 38 tahun datang ke IGD RS dengan keluhan mimisan sulit berhenti sejak 4 hari sebelumnya. Dikeluhkan juga sering timbul lebam-lebam di kulit lengan atas dan paha bawah kanan sejak 3 bulan terakhir. Tidak ada riwayat perdarahan atau lebam sebelumnya. Tidak ada riwayat alergi obat atau makanan. Pemeriksaan fisik didapat conjunctiva tidak pucat, bekas perdarahan di hidung kanan , paru dan jantung normal, Hepar/ lien tidak teraba, ekstremitas dijumpai purpura pada regio humeri kiri dan femoralis kanan. Dilakukan pemeriksaan darah rutin dengan hasil Hb 15 gr/dL, Ht 45, 1%, Lekosit 6700/ mm3 dan trombosit 17.000 / mm3. Morfologi Darah Tepi ditemukan Giant trombosit. Dokter menyimpulkan pasien tersebut kemungkinan menderita Immune Thrombocytopenia Purpura. Untuk medukung diagnosis tersebut dianjurkan pemeriksaan lanjutan

SKENARI

MEMAR PADA LENGAN DAN TUNGKAI

Seorang anak laki-laki berusia 4 tahun dibawa orangtuanya berobat ke RS YARSI dengan keluhan lutut kanan bengkak dan nyeri sehingga sulit untuk berjalan sejak 2 hari sebelumnya. Ibunya mengatakan bahwa sebelumnya sering ada memar pada lengan dan tungkainya. Keluhan tidak didahului oleh adanya trauma. Penderita tampak sehat, tidak ada kejang, penurunan kesadaran ataupun pucat, terdapat hematoma pada kedua tungkai serta hemarthrosis pada genu dextra. Penderita sudah sering mengalami keluhan serupa dan selalu mendapat *replacement therapy* berupa injeksi konsentrat faktor VIII. Pasien ditangani secara komprehensif karena sudah terjadi komplikasi berupa sinovitis dan diduga sudah terbentuk antibodi terhadap faktor VIII.

SKENARIO 4

BADAN BERTAMBAH LEMAH DAN PUCAT

Seorang anak perempuan berusia 6 tahun datang ke RS YARSI dengan keluhan utama badan bertambah lemah dan pucat sejak beberapa bulan terakhir. Pada pemeriksaan fisik : berat badan 14,9 kg, tampak pucat dengan perut agak membesar, muka memperlihatkan tanda *facies Cooley*, terdapat hepatomegali dan splenomegali. Pemeriksaan laboratorium menunjukkan tanda anemia hemolitik kronik, sumsum tulang memperlihatkan keaktifan sistem eritropoetik yang hebat. Hasil elektoforesis Hb menunjukkan HbF 48% dengan HbE 50%. Rontgen tulang kepala menunjukkan gambaran *hair standing on end appearance*. Dengan dasar itu dokter menegakkan diagnosis talasemia-β Hb E. Pemeriksaan terhadap orangtua menunjukkan ayah penderita talasemia Hb E dan ibu penderita talasemia minor. Pasien direncanakan mendapat transfusi dan terapi kelasi besi. Dokter menjelaskan kemungkinan hemosiderosis dan *delayed puberty* pada pasien ini dan kemungkinan splenektomi di kemudian hari, serta melakukan konseling genetik pada orangtua bila ingin mempunyai anak lagi.

SKENARIO 5

DEMAM BERDARAH DENGUE

Nina, seorang anak perempuan berusia 7 tahun, sudah 5 hari tidak masuk sekolah karena demam tinggi terus menerus yang hanya turun sedikit bila diberi penurun panas. Hari ini sejak pagi Nina sudah tidak demam sehingga orangtuanya merasa tidak perlu kontrol lagi, tapi karena Nina mengeluh masih lemas dan nyeri kepala serta nyeri perut maka Nina tidak masuk sekolah lagi. Sore harinya Nina makin lemas sehingga orangtuanya membawa Nina ke UGD RS YARSI.

Menurut orangtuanya Nina tidak mimisan atau mengalami gusi berdarah. Dokter mencurigai Nina menderita **Demam Berdarah Dengue stadium I** dan meminta pemeriksaan darah dan rontgen dada serta menyatakan Nina perlu dirawat inap segera. Dokter juga menjelaskan bahwa penyakit Nina disebabkan oleh infeksi **virus Dengue** yang merupakan **arbovirus** dan ditularkan oleh **vektor** nyamuk *Aedes aegypti*.

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REVIEW

Aging of the hematopoietic system

Hans-Willem Snoeck

Purpose of review
Aging of the hematopoietic system is associated with myeloid malignancies, anemia and immune dysfunction. As hematopoietic stem cells (HSCs) generate all cells of the hematopoietic system, age-associated changes in HSCs may underlie many features of the aged hematopoietic system. Recent findings on age-associated changes in HSCs are reviewed here.

Recent findings
Aged HSCs are myeloid biased, have acquired DNA damage and are functionally compromised. However, overall function of the HSC compartment is well maintained through age-associated expansion of HSCs. Many age-related changes in the hematopoietic system, in particular the clonal myeloid bias of HSCs and the decrease in B and T-cell development, in fact begin during development. Furthermore, HSCs possess specific protective mechanisms aimed at maintaining their number, even at the expense of accumulating damaged cells.

Summary
We argue that age-related changes in HSCs and in the hematopoietic system may not entirely be due to a degenerative aging process, but are the result of developmental and stem cell-protective mechanisms aimed at maximizing fitness during reproductive life. These mechanisms may be disadvantageous later in life as damaged HSCs accumulate and establishment of responses to neoantigens becomes compromised because of the reduced generation of naive T and B cells.

Keywords
aging, development, hematopoietic stem cells

INTRODUCTION

Similar to most organs and tissues, the hematopoietic system shows evidence of aging, which is associated with increased incidence of myeloid malignancies, myelodysplasia, myeloproliferative neoplasms, chronic anemia and multifactorial immune dysfunction [1–3]. Furthermore, donor age is a major negative prognostic factor in the outcome of allogeneic bone marrow transplantation [4]. As stem cells assure tissue maintenance, it is logical to infer that hematopoietic stem cell (HSC) dysfunction underlies aging of the hematopoietic system.

THE FUNCTIONAL PHENOTYPE OF AGED HEMATOPOIETIC STEM CELLS

In mice, aging is associated with expansion of the HSC compartment [5–8], such that old bone marrow can even outcompete equal amounts of young bone marrow [9]. Furthermore, hematopoietic reconstitution from aged HSCs is myeloid-biased compared with reconstitution by young HSCs [8,10–12]. The most rigorous functional analysis of aged HSCs was reported by Dykstra *et al.* [7], who showed that aged HSCs are, on a per cell basis, inferior to young HSCs in their capacity to reconstitute lethally irradiated recipients and to self-renew, as assayed in serial transplantation studies. Furthermore, homing [13] and in-vitro proliferation in stromal cocultures were reduced. Reconstitution of the HSC compartment by aged HSCs was normal [14&]. Intravital microscopy suggested that early progenitors from aged mice localize further from the presumed osteoblastic niche in the bone marrow than cells from young mice, and display more dynamic changes in cell shape [15]. Furthermore, upon adhesion to fibronectin, early progenitors from aged mice show reduced polarization of the

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Curr Opin Hematol 2013, 20:355–361

DOI:10.1097/MOH.0b013e3283623c77

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KEY POINTS

- Aging of HSCs is associated with expansion of stem cell number, decreased function of individual stem cells, increased myeloid bias, decreased polarity, and increased DNA damage. The overall function of the HSC compartment is maintained, however.
- These changes are predominantly intrinsic.
- Expansion of the stem cell compartment, increased myeloid bias, and a decrease in lymphopoiesis start early in life, and may therefore be developmentally programmed.
- Hematopoietic stem cells possess intrinsic stem cell-protective mechanisms that preserve the function of the stem cell compartment as a whole, but may be accompanied by accumulation of damaged stem cells.
- Both developmentally programmed changes and stem cell-protective mechanisms contribute to age-related changes in HSC function and in the hematopoietic system.

microtubule cytoskeleton compared with cells from young mice [15]. Distinct niche interactions are also suggested by the observation that progenitor cells from old mice are mobilized more efficiently [16]. Together, most available data suggest intrinsically compromised function of individual aged HSCs, but maintenance of overall function of HSCs as a population. Several lymphoid precursors, such as common lymphoid progenitors (CLPs) and, in particular, pre-B cells are depleted in the bone marrow of old mice [3]. Lymphopoiesis is not only affected by HSC-intrinsic changes, however. The age-associated decline in pre-B cells appears mostly caused by the aged microenvironment [17], whereas T-cell development is severely curtailed by thymic involution [18]. Lymphocyte number is maintained, however, because homeostatic proliferation fills the void with antigen-experienced cells (memory T cells; marginal zone, B1 and memory B cells) [2,3,19].

Similar to mice, the frequency of human HSCs increases with age, and the HSC compartment shows a myeloid bias at the population level when assayed by xenotransplantation in immunodeficient mice [20].

CONSEQUENCES OF AGING OF HEMATOPOIETIC STEM CELLS

The negative impact of donor age on the outcome of allogeneic bone marrow transplantation appears mostly due to higher incidence and severity of graft-versus-host disease, and not to an engraftment defect [4]. It is tempting to speculate, however, that the increased incidence of myeloid malignancies in the elderly can be traced back to the myeloid bias of HSCs. HSCs, the only persistent lineage of hematopoietic cells, serve as a repository for accumulating DNA mutations that can confer abnormal self-renewal properties to downstream progenitor cells, leading to leukemia [1]. Furthermore, the lower incidence of lymphoid malignancies originating from developing B and T cells in the aged compared with the young [21] may be caused by impaired lymphopoiesis. The fact that the most prevalent hematological malignancy in the elderly is chronic lymphocytic leukemia (CLL) [22] is often overlooked in this context, however. CLL is a malignant, clonal B-cell expansion with the phenotype of antigen-experienced B cells. Although originally thought to be driven by chronic stimulation by as yet undefined antigens [22], recent evidence suggests that cell autonomous signaling through the B-cell receptor (BCR) in response to internal BCR epitopes drives this malignancy [23▪]. Nevertheless, xenotransplantation studies in immunodeficient mice have shown that the propensity to generate oligoclonal or monoclonal B-cell development originates in HSCs of CLL patients [24]. In this context, is it also interesting to note that in mice with a transgenic BCR, B cells with a phenotype of antigen-experienced cells and bearing the endogenous BCR increase with age [25]. Transplantation of purified HSCs from old mice to young mice transferred these altered B-cell specificities. Furthermore, transplantation of small numbers of young HSCs or treating recipients with anti-interleukin-7 antibodies, two approaches that compromise the B-cell regenerative capacity of the hematopoietic system, also skewed the B-cell population toward antigen-experienced cells expressing the endogenous BCR [26]. It is therefore plausible to hypothesize that aging of HSCs, and therefore their reduced lymphoid potential and overall functional compromise, may contribute to a skewed B-cell repertoire and to a propensity to develop CLL or its precursors.

MOLECULAR PHENOTYPE OF AGED HEMATOPOIETIC STEM CELLS

Genome-wide expression studies comparing HSCs from young and old mice showed that in aged HSCs, expression of genes involved in myeloid development was increased whereas expression of genes involved in lymphopoiesis was decreased, a finding consistent with their myeloid bias [8]. Furthermore, gene sets associated with inflammation were increased in aged HSCs [8,27]. Young and aged HSCs differ in epigenetic regulation. Aged HSCs show

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general hypermethylation [14▪]. This was surprising, as aging in most tissues is associated with hypomethylation [28]. Interestingly, however, differentially methylated regions were enriched in genes expressed in downstream lineages and not, or less so, in HSCs themselves, and included genes involved in erythropoiesis and lymphopoiesis. Furthermore, a fraction of these genes are targets of the polcycomb repressor complex (PRC)2, and expression of several PRC2 components was slightly reduced in aged HSCs [14▪,29]. Downregulation of genes involved in transcription and chromatin regulation, as well as concomitant misexpression of lymphoid transcripts such as Igκ germline transcripts, was observed in another study [27]. A fraction of HSCs in aged mice also display lower histone H4 lysine acetylation (AcH4K16) [30▪▪], providing further evidence for changes in epigenetic regulation. Aged HSCs express higher levels of the RhoGTPase cdc42, and this increased expression was associated with the decreased polarity and decreased AcH4K16 observed in aged HSCs compared with young HSCs [30▪▪]. Finally, an age-associated increase in DNA damage as measured by γH2AX foci has been observed in HSCs, suggesting a role for accumulated DNA damage [31].

THE ROLE OF PROLIFERATIVE HISTORY

Proliferation of most normal cells ultimately leads to senescence. Adult HSCs are remarkably quiescent, however, though they can reversibly enter and exit cell cycle, even in steady state [32,33,34▪]. Given their relative quiescence, the expansion of the normally cycling aged HSC compartment is unlikely to be explained by cellular senescence. Furthermore, despite earlier suggestions [35], the p16INK4a locus, a prime regulator of senescence, remains epigenetically repressed in aged HSCs [29].

Proliferation is accompanied by telomere shortening. Humans have shorter telomeres than inbred mice, and progressive telomere shortening is observed in the peripheral blood, a proxy of telomere shortening in HSCs [36,37]. Although genetic telomere dysfunction in humans causes dyskeratosis congenita, a disease with a high incidence of bone marrow failure, and although acquired severe aplastic anemia is associated with short telomeres [36,37], the role of telomere shortening in physiological aging of human HSCs has not been determined [38]. HSCs fail in late generation telomerase-deficient mice [39]. However, maintenance of mouse HSCs is not dependent on telomeres, as increasing telomerase activity in HSCs through overexpression of telomerase does not rescue HSCs from exhaustion induced by serial transplantation [40]. Other mechanisms must therefore be invoked to explain HSC exhaustion after serial transplantation.

Nevertheless, forced proliferation of mouse HSCs by serial transplantation [7], transplantation of very low numbers of HSCs [14▪] or repeated administration of 5-fluorouracil [14▪] induced changes similar to those observed in physiological aging, namely lower reconstitution capacity and myeloid bias. These findings may suggest a contribution of proliferative history to age-related changes in HSCs. It should be noted, however, that in serial transplantation studies, the chronological age of young HSCs that underwent three rounds of serial transplantation (approximately 20 months) was similar to what is considered 'aged' in C57BL/6 mice [7]. It is therefore unclear to what extent functional changes in the HSC compartment in serial transplantation studies are caused by chronological aging, or by forced proliferation, or by a combination of both. Furthermore, forced proliferation of HSCs may differ from physiological aging. Repeated 5-fluorouracil administration, although inducing a functional phenotype similar to that of aged HSCs, was associated with global hypomethylation. On the other hand, physiological aging of HSCs was associated with global hypermethylation, although a fraction of differentially methylated regions was shared between physiologically aged HSCs and HSCs subjected to forced proliferation [14▪]. Thus, although proliferative history may contribute to physiological HSC aging in mice, the latter is not fully modeled by forced cycling and expansion of HSCs.

THE ROLE OF INFLAMMATION

Aging is characterized by a state of low-level inflammation, that may both cause and perpetuate the aging process [41]. The aging hematopoietic system may itself be a source of inflammatory mediators. Thymic involution leads to a decreased pool of naive T cells. Through peripheral expansion, memory cells fill the void in the T-cell pool in aged individuals [19,42]. This accumulation of senescent memory cells, by virtue of their constitutive production of inflammatory cytokines, has been linked to the general state of low-level inflammation and frailty that characterizes aging ('inflammaging') [42]. A common feature of genome-wide expression studies of aged HSCs is the preponderance of genes involved in inflammation among upregulated genes [8,27]. Furthermore, recent work has shown that HSCs participate in systemic inflammatory responses [43] and respond directly to inflammatory cytokines

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such as interferons [44,45], and that deletion of mechanisms that dampen the effect of interferons on HSCs leads to enhanced cycling and exhaustion [46,47]. Inflammation may therefore contribute to HSC aging. However, it is also possible that the increased inflammatory gene expression in HSCs is a reflection of the inflammatory environment in aged individuals, and not necessarily causally related to age-related changes in HSCs.

THE ROLE OF STEM CELL-PROTECTIVE MECHANISMS

Continuous exposure to extrinsic (such as low-dose environmental irradiation) or intrinsic [such as reactive oxygen species (ROS) generated by cellular metabolism] stressors can lead to stem cell dysfunction, and affect tissue integrity. HSCs are endowed with specific protective mechanisms, however. Quiescence likely protects from senescence [34▪]. HSCs are exquisitely sensitive to ROS, predominantly produced by mitochondrial respiration [48]. Mechanisms that reduce ROS production and/or increase ROS scavenging in HSCs include Atm [49], Foxo transcription factors [50] and the reliance on glycolysis for ATP production [51]. HSCs have an increased capacity of autophagy in response to stress compared with progenitor cells, which undergo apoptosis in the same conditions [52▪▪]. Interestingly, autophagy and ROS production and scavenging are regulated by members of the Foxo family [50,52▪▪], which are involved in lifespan regulation in *Caenorhabditis elegans* [53], suggesting that HSCs have adopted organismal maintenance mechanisms of lower organisms. HSCs are more radioresistant than myeloid progenitors, among others, because of robust induction of DNA damage checkpoints and high expression of prosurvival genes and p21. Because of their quiescent nature, HSCs use the error-prone nonhomologous end-joining (NHEJ) pathway, whereas cycling progenitors use homologous recombination to repair irradiation-induced DNA double-strand breaks. However, even after HSCs are induced to cycle, and partially rewire their DNA repair toward homologous recombination, they do remain more radioresistant than progenitors [54]. The use of the error-prone NHEJ leads to persistent DNA damage in HSCs, and may cause malignancy, although the latter has not been formally demonstrated [54]. The gene *Batf* is induced upon DNA damage, inhibits self-renewal, and drives the cells toward lymphoid differentiation. As lymphoid-biased HSCs appear more sensitive to the effect of *Batf*, this mechanism may contribute to depletion of lymphoid biased HSCs and relative maintenance of myeloid biased HSCs [55]. Taken together, most available evidence suggests that the HSC compartment is maintained through attempted repair at the cost of retaining damaged cells rather than replacing these by enhanced self-renewal.

Aging might be caused by failure of these protective mechanisms. However, there is little evidence that stem cell-protective mechanisms overtly fail in aging HSCs. Increased autophagy is maintained in aged HSCs [52▪▪]. Genome-wide expression studies did not reveal major changes in genes essential for maintenance of quiescence in HSCs [8,27], and HSC cycling does not increase with age. Although genetic deletion of stem cell-specific protective mechanisms results in stem cell dysfunction, these phenotypes may represent frank stem cell failure rather than physiological aging [34▪]. For example, knockout mice in which components of DNA repair mechanisms were deleted show mostly defects in downstream progenitor cells in steady state, and HSC function is only compromised after transplantation of limiting numbers of HSCs [31]. Myeloid/lymphoid skewing is not observed in these knockout mouse models [56]. Thus, failure of mechanisms that protect HSCs from various forms of stress is unlikely to explain age-related changes in HSCs.

An alternative hypothesis is that age-related changes in HSCs may at least in part be a result of the very mechanisms aimed at maintaining function of the overall HSC compartment. As mentioned before, the HSC compartment is geared toward maintenance through prevention of damage by ROS, and through attempted repair rather than replacing HSCs by enhanced self-renewal. This mode of maintenance of the HSC compartment may have evolved because of the apparently extreme sensitivity of the HSC compartment to enhanced cycling in steady state. Although HSCs have enormous self-renewal potential after transplantation [57▪], enhanced HSC cycling in steady state is associated with rapid exhaustion in multiple mouse knockout models in which quiescence of HSCs was disrupted [34▪]. The role of quiescence in HSC maintenance is not well understood, however, as in some knockouts, such as Cdkn2c$^{-/-}$ mice, enhanced HSC cycling was not associated with exhaustion [58]. It has been proposed that quiescence is required to prevent inappropriate differentiation, and therefore loss of HSCs [34▪]. Thus, maintaining low levels of self-renewal in steady state and favoring attempts at repair over disposal of damaged HSCs could lead to an HSC compartment that expands with age and maintains its overall function, but in which the function of individual HSCs is compromised.

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THE ROLE OF DEVELOPMENTAL PROGRAMMING

The progressive myeloid bias of the HSC compartment, which may be caused by the higher intrinsic self-renewal capacity of myeloid-biased HSCs [11,12], likely serves an evolutionary purpose as well. Benz *et al.* [57▪] showed that although in fetal liver balanced (*b*) HSCs predominate, the frequency of myeloid-biased (*a*) HSCs increases as development proceeds. CLPs derived from *a*-HSCs were defective and expressed lower levels of B-lineage-specific genes, a phenotype similar to that of aged CLPs [57▪]. The adaptive immune system develops early in life to establish antigen-specific responses to the multitude of antigens encountered during extrauterine life, while preventing responses against self. The cost of this process is iterative recombination of T and B-cell receptor loci accompanied by massive proliferation and deletion of the majority of the cells, which carries the risk of malignancy. Indeed, acute lymphoblastic leukemia is predominantly a disease of children [21]. Once the immune repertoire is established, cessation of recombination and establishment of vigorous and rapid memory responses likely benefits fitness. Thymic involution should probably be viewed in this context as well. Supporting this notion is the fact that not only changes in the types of B and T cells produced [59], but also the decrease in B-cell development [59], the emergence of *a*-HSC clones [57▪]

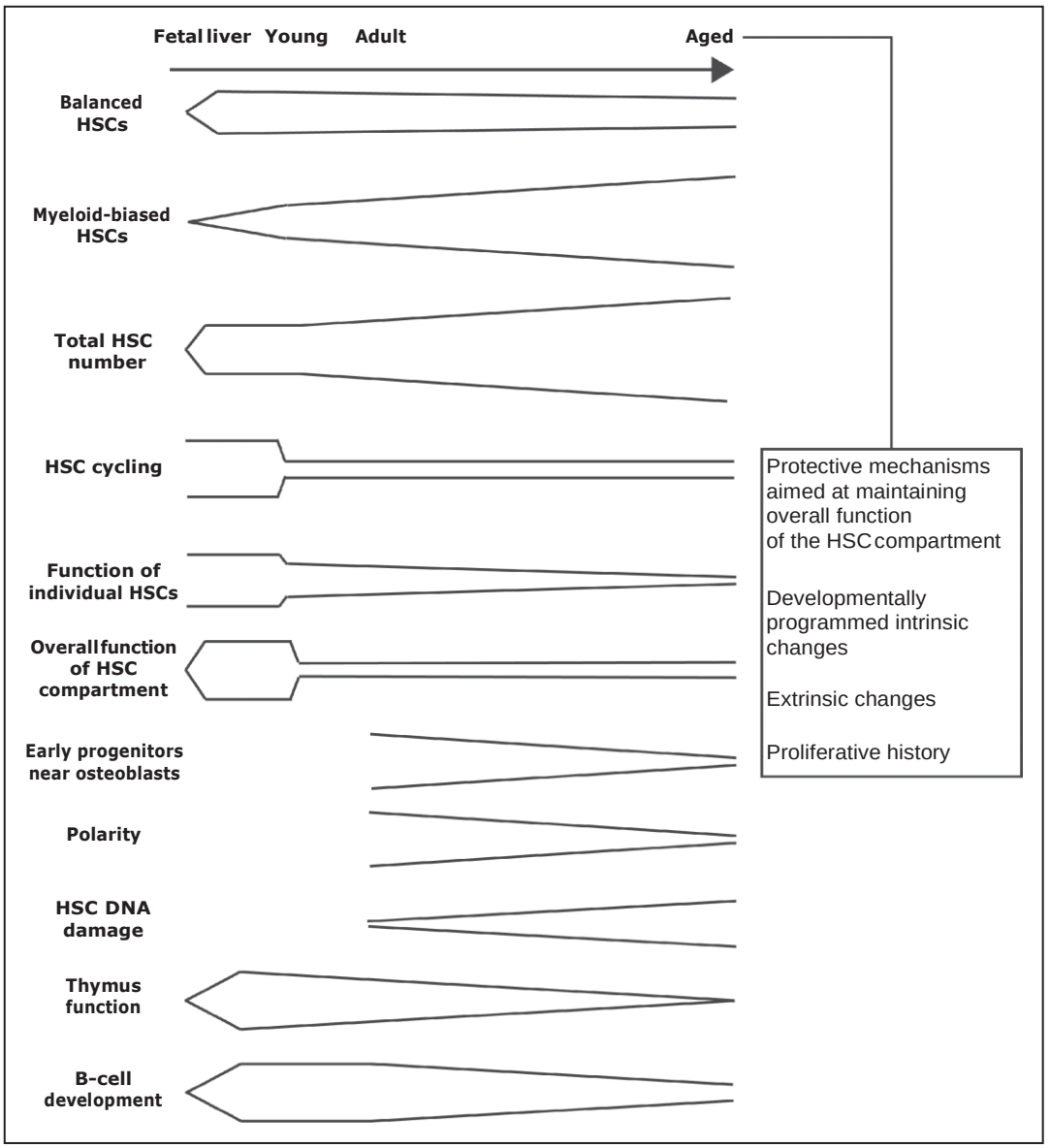


FIGURE 1. Schematic overview of functional changes in the hematopoietic system throughout development and aging. HSC, hematopoietic stem cell.

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and thymic involution [59– 61] start very early in life, and are therefore likely a result of developmental programs, and not of aging *per se*.

It has recently been shown that most HSCs reside in the perivascular bone marrow niche, whereas very early lymphoid progenitors reside in the osteoblastic niche [62&&,63&&]. It is not known whether *a*-HSCs and *b*-HSCs occupy distinct niches, but it is possible that the localization of aged early progenitors farther away from the osteoblasts is a reflection of a shift toward myelopoiesis [15]. Furthermore, although the argument has been made that epigenetic changes contribute to aging of stem cells [14&,27,64], epigenetic regulation is critical for development. The generation of induced pluripotent state cells (iPSCs) from somatic cells involves near-complete epigenetic rewiring of the cells toward a developmental 'ground' state [65]. The recent demonstration that HSCs in mice derived from iPSCs generated from aged HSCs are functionally 'young' suggests that aging of HSCs carries a large epigenetic component and is reversible. The argument could be made, as was acknowledged by the authors, that the data may be a reflection of the selection of a subset of HSCs that are not or are less affected by age-associated damage [66]. However, Florian *et al.* [30&&] showed that pharmacological inhibition of the RhoGTPase Cdc42 allowed rejuvenation of HSC function in terms of polarity, long-term repopulation capacity and localization closer to the osteoblastic niche. The fact that the AcH4K16 staining pattern also appeared 'younger' suggests a reversal of epigenetic changes, which could at least in part be developmentally programmed.

CONCLUSION

Although it is possible that proliferative history contributes to the aging of HSCs, part of the functional phenotype of the aged hematopoietic system may be the result of intrinsic and extrinsic developmental and stem cell-protective mechanisms aimed at maximizing fitness during reproductive life (summarized in Fig. 1). Hematopoietic aging might therefore be an example of antagonistic pleiotropy, which posits that traits that confer fitness prior to and during the reproductive age can be detrimental after reproductive age and contribute to aging [67]. Hematopoietic regulation is geared toward maintaining a functional HSC compartment with optimal homeostatic responses to stress and toward generating an adaptive immune system early in life while avoiding lymphoid malignancies during reproductive age. These processes may decrease fitness later in life, however, as subfunctional; damaged HSCs accumulate and establishment of responses to neoantigens (tumor-associated or infectious) becomes problematic because of the reduced generation of naive T and B cells.

Acknowledgements

Part of the author's work on aging was supported by NIH grant RO1 AG029262.

Conflicts of interest

There are no conflicts of interest.

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Blood clots in COVID-19 patients: Simplifying the curious mystery

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ABSTRACT

The universal phenomenon of blood clotting is well known to be protective in external cellular/ tissue injury. However, the emergence of unusual thrombotic presentations in COVID-19 patients is the real concern. Interaction of the spike glycoprotein with ACE2 receptor present in the host cell surface mediates the entry of SARS-CoV-2 causing COVID-19 infection. New clinical findings of SARS-CoV-2 pathogenesis are coming out every day, and one such mystery is the formation of mysterious blood clots in the various tissues and organs of COVID-19 patients, which needs critical attention. To address this issue, we hypothesis that, high ACE2 expression in the endothelium of blood vessels facilitates the high-affinity binding of SARS-CoV-2 using spike protein, causing infection and internal injury inside the vascular wall of blood vessels. This viral associated injury may directly/indirectly initiate activation of coagulation and clotting cascades forming internal blood clots. However, the presence of these clots is undesirable as they are responsible for thrombosis and need to be treated with anti-thrombotic intervention.

Background

Coronavirus Disease (COVID-19), since its emergence from Wuhan province, China in December 2019, now spreading to 213 countries worldwide, forcing the World health organization to declare this outbreak a global pandemic on 11 March 2020 [1]. COVID-19 is caused by highly infectious, severe acute respiratory syndrome coronavirus (SARS-CoV-2), infecting more than 36 million individuals, with 1,060,563 reported deaths as of 8 October 2020 [2]. The understanding of this novel virus and disease evolves sequentially in the past seven months. Initially, thought to transmit by droplets or aerosols causing fever as classical clinical symptoms, mainly in old age or immunocompromised individuals. However, the dynamics of COVID-19 keeps on evolving with the emergence of different SARS-CoV-2 strains. Evidence of airborne mode of SARS-CoV-2 transmission [3], asymptomatic clinical presentations along with extra-pulmonary manifestations [4] are the real concern.

SARS-CoV-2 is a single-stranded, positive-sense RNA virus having envelope, glycoprotein, and spike protein. Being a respiratory virus, SARS-CoV-2 enters inside the human body and infect the lungs as a primary and predominant organ [5]. The entry is mediated by the binding of the receptor-binding domain (RBD) of the S1 subunit of the viral spike protein with the host angiotensin-converting enzyme 2, (ACE2) receptor primarily expressed in the type II pneumocytes, serving as a viral reservoir [6,7]. Usually, COVID-19 presented with fever, sore throat, dry cough, and shortness of breath as common clinical manifestations [8], however asymptomatic cases are also being reported which are more critical to diagnose. ACE2 is also found to be expressed in the oral, nasal mucosa, epithelial cells of lungs, kidney, and heart, enterocytes of the small intestine, and in the endothelial cells of blood vessels [9]. The SARS-COV-2 associated extra-pulmonary manifestations are encephalitis, rashes on the skin, meningitis, conjunctivitis, acute hepatic, and renal injury.

Surprisingly, autopsies of COVID-19 patients have revealed clots in the small vessels of the lungs, heart, liver, and kidney which are responsible for strokes and heart attacks [10]. More than 33% of critical COVID-19 patients' are reported with critically high levels of blood clotting or elevated levels of D-dimer [11]. The development of these mysterious clots causing coagulation abnormalities and thrombosis is the real concern and needs to be addressed. So, we hypothesis the possible mechanism for the formation of the vascular blood clots in COVID-19 patients.

Origin of hypothesis

The hypothesis for the formation of blood clots in the vessels is retrieved from the classical concept of blood clotting. The mechanism of blood clotting is like a two-edged sword, wherein the case of severe

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https://doi.org/10.1016/j.mehy.2020.110371
Received 21 August 2020; Received in revised form 8 October 2020; Accepted 21 October 2020
Available online 6 November 2020
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Please cite this article as: Sourav Biswas, *Medical Hypotheses*, https://doi.org/10.1016/j.mehy.2020.110371

external injury, clotting is very crucial for preventing the blood loss, whereas, in the case of internal blood vessels injury, it, unfortunately, leads to the formation of blood clots, causing vascular blockades and thrombosis, expanding to every organ leading to severe and fatal outcomes.

The above concept is substantiated by the following three facts:

)a) Recognition of ACE2 receptor-expressing endothelial cells of the blood vessels by spike protein of SRAS-CoV-2.
)b) Direct injury to the endothelial cell by SARS-CoV-2 infection resulting in vascular damage.
)c) Indirect damage due to immune-mediated cytokine release syndrome (CRS) causing inflammation and cell death.

To protect the direct and/or indirect damage caused by SARS-CoV-2 to endothelial cells lining the blood vessels, host innate defensive mechanism of blood clotting activates, recruiting the activated platelets at the injury site to form a clot which although reduce the damage but negatively may lead to obstruction of blood vessels and vasoconstriction causing more damage.

The virus enters into the peripheral blood causing viremia and gets transmitted to the different organs such as the heart, kidney, gastrointestinal tract resulting in multiple organ failure. As it is evident that blood clots were observed in both live and dead COVID-19 patients, so it is out most interesting to decode the mystery.

Hypothesis statement

Considering the above facts and recent unusual reports, a hypothesis develops for the blood clots formation in the COVID-19 patients (Fig. 1), states that *"Due to an internal injury in the endothelium of blood vessels, either directly by SARS-CoV-2 infection (co-expression and binding of the spike protein with the ACE2) or my virus-mediated inflammatory immune response, may result in vasoconstriction and the activation of coagulation and blood clotting pathways, resulting in the formation of blood clots"*.

Theoretical evaluation and validation

During COVID-19 infection, SARS-CoV-2 enters into the systemic circulation and binds with the ACE2 expressing endothelial cells (endothelium) lining the blood vessels. Binding facilitates the virus internalization, causing infection and injury in the vascular wall of blood vessels. The vascular injury might result in vasoconstriction, which may further reduce the blood flow at the site of injury. Also, injury to endothelial cells reduces the expression of fibrinolytic heparin and thrombomodulin. Conversely, high expression and secretion of the Von Willebrand factor enhance the aggregation of platelets at the site of injury in blood vessels and activate the coagulation cascade for the formation of blood clots.

Immediately within a few seconds of endothelial cells injury in a blood vessel, platelets along with collagen, recruit at the injury site to swell and aggregate. Soon the coagulation is initiated and fibrin strands begin to intersperse among the wound to form a complete platelet plug. Viruses like Dengue and Herpes simplex virus (HSV) are known to infect endothelial and circulating blood cells, activating coagulation cascade by promoting tissue factor [12]. Interestingly, lysis of fibrin known as fibrinolysis by fibrinolytic molecule plasminogen and plasmin proved to induce deleterious inflammation and defective fibrin clot formation in Influenza A viruses (IAV) [13]. In addition to viral stimulation, binding of an extracellular proteolytic enzyme known as urokinase-type plasminogen activator (uPA) with its receptor, uPAR is crucial for the activation of plasminogen to plasmin as reported in various malignancies [14]. Detrimental inflammation in the endothelial cells may initiate the cascade of cytokine release and subsequently leads to the blood vessel injury.

Similarly, the SARS-CoV-2 induced vascular trauma/injury, activates the platelets exposed endothelium or collagen following the intrinsic pathway. Following the injury to blood vessels, near-by platelets stick to the vascular proteins, get degranulated, releasing prothrombin activator, serotonin, adenosine diphosphate (ADP), and thromboxane A2 for further activation of platelets. The mechanism for the formation of clots in the blood vessels may start sequentially by 12 clotting factors, i.e. activating the factor XII, converting prothrombin to thrombin and later fibrinogen to long and insoluble fibrin which may entangle with

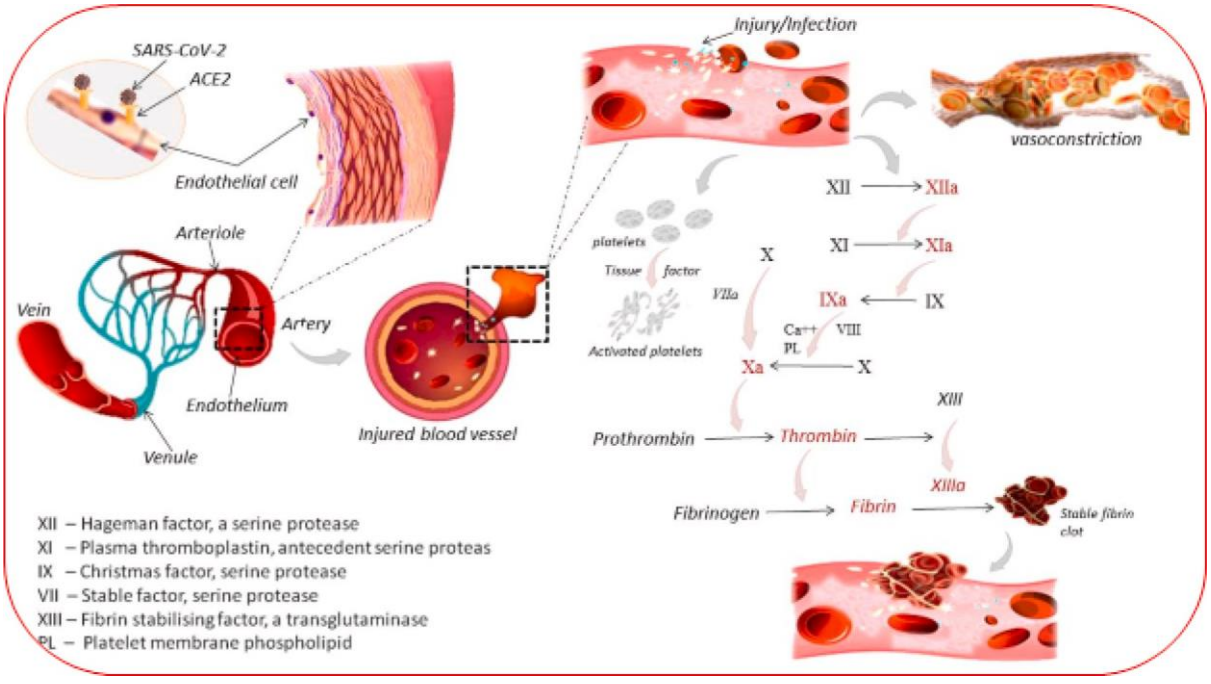


Fig. 1. Schematic representation showing the mechanism of clot formation in the blood vessels when the endothelial cells rich in ACE2 receptors are targeted by SARS-CoV-2 and resulted in the internal blood vessel injury, resulting in the cascade of blood clot formation.

platelets by covalent cross-linking, forming a stable interlocking fibrous network of a fibrin clot at the site of injury. This may slow down the blood flow, but platelets in the clot begin to shrink to initiate the wound healing process with intrinsic and extrinsic coagulation pathways. However, the upregulation of the expression of fibrinogen subunits FGA, FGB, and FGG also plays a very significant role in the formation of the clot. Various thrombotic complications and coagulation abnormalities are associated with COVID-19 like sepsis-induced coagulopathy (SIC), disseminated intravascular coagulation (DIC), venous thromboembolism (VTE), pulmonary embolism (PE), micro-thrombosis, microvascular thrombosis, and thrombotic micro-angiopathy. Intense endothelial inflammation may be the involved mechanism leading to microvascular thrombosis as suggested in lung pathology contributing to ARDS [15]. SIC is hypercoagulability, characterized by elevated fibrinogen and D-dimer levels causing endothelial dysfunction, micro-thrombosis, and stroke [16].

Additionally, vasoconstriction has an inverse relation with ACE2. During systemic infection, the ACE2 expressed blood vessels' endothelial cells, might attach to the viral spike protein resulting in the unavailability of ACE2. Renin-angiotensin-aldosterone system (RAAS) may drive the formation of micro-thrombin in COVID-19 patients stimulating Angiotensin II (Ag II) to induce tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) expression by endothelial cells. Ag II acts on the CNS to increase vasopressin production which causes vasoconstriction. Depletion of ACE2 by SARS-CoV-2, PAI-1/tPA imbalance, and a hyper-coagulable state may favor tissue injury and stroke [17]. This may explain the unresolved mystery of unresolved fibrin deposits in the alveoli of patients with general ARDS [18].

ACE2 converts Ag II to Ag (1–7), protecting endothelial cell function and prevent early atherosclerosis which can be caused by a clot in the blood vessels [19]. Profound hypoxemia in the pulmonary capillaries may result in the activation of hypoxia-inducible factors (HIFs) resulting in inducing or inhibition of TF and PAI-1 respectively, and vasoconstriction thereby promoting vascular occlusion [20–22].

The deposition of the C56-9 component of the complement system in the damaged vessel results in micro thrombosis as an anti-phospholipid syndrome [23]. Neutrophil extracellular traps (NET) are associated with elevated levels of histones, activating increased thrombin production [24]. In a study including 362 closed COVID-19 cases from Italy, high mortality attributed to pulmonary embolism (PE) and pulmonary thrombosis with VTE and ischemic stroke as primary and DIC as a secondary outcome. Thromboembolic events occurred in 28 (7.7%) cases, with VTE in 16 (36%), PE in 10 (33%) and, DIC in 8 (2.2%) patients [25]. High-risk coagulation abnormalities are associated with an elevated concentration of D-dimer and a reduction in platelet count [11]. Thrombotic microangiopathy in the lungs autopsies showing aggregates of CD4 around thrombosed small vessels and are significantly associated with hemorrhage. [26]. VTE may develop via immunologic activation of intravascular and platelet-releases thrombin. Severe derangement of hemostasis, accompanied by reduced platelet count and fibrinogen, may explain the events of venous thromboembolism supporting hypercoagulability in COVID-19 positive patients [27]. Incidence of VT increase between 25% and 49% in severe COVID-19 patients, with pulmonary embolism being the most common thrombotic complication [28,29]. Microvascular thrombotic complications are indicative of a strong interaction between the SARS-CoV-2 and coagulation. More than 80% of lung autopsies reported platelet–fibrin thrombi, especially in the small pulmonary vasculature [30]. The presence of antiphospholipid antibodies is a serious complication causing thrombotic stroke in young patients [31].

SO, in COVID-19 patients, the SARS-CoV-2 mediated endothelial inflammation, thrombin generation, platelet, and leukocyte recruitment, complement activation, and the initiation of innate and adaptive immune responses, forming clots, culminate in immunothrombosis, ultimately resulting in thrombotic complications, stroke, and finally death.

Discussion & conclusion

Based on the literature and clinical observation of mysterious clots reported in the COVID-19 patients, expression of ACE2 in the endothelium of blood vessels, blood clotting pathways, interaction of the SARS-CoV-2 spike protein with host ACE2, the pathogenesis of SARS-CoV-2, and the role of ACE2 in RAS, we can hypothesize and end with the conclusion that the mysterious clots reported in the COVID-19 patients may be due to the binding of the spike protein of SARS-CoV-2 with the ACE2 receptor expressed in the endothelial cells of blood vessels which may cause, vasoconstriction and activation of the intrinsic pathway of coagulation and eventually results in the formation of blood clots.

CRediT authorship contribution statement

Saurav Biswas: Conceptualization, Data curation, Investigation, Methodology, Writing - original draft. **Vikram Thakur:** Conceptualization. Writing - original draft, Data curation, Investigation, Methodology, Resources, Software. **Parneet Kaur:** Writing - review & editing. **Azhar Khan:** Formal analysis, Investigation Validation, Visualization. **Saurabh Kulshrestha:** Validation, Visualization, Funding acquisition, Investigation, Project administration. **Pradeep Kumar:** Conceptualization, Writing - review & editing, Formal analysis, Investigation, Validation, Visualization, Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

Special thanks to Prof. Prem Kumar Khosla, Vice-Chancellor, Shoolini University, Solan for providing financial support and necessary facilities.

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23. *Onchocerca* vo/w/Us (Leuckart 1893)

Introduction

Onchocerca volvulus is a vector-borne filarial nematode. The adult worm locates to a single niche in the subcutaneous tissues. Its offspring, microfilariae, migrate throughout this tissue, inducing injury to a variety of anatomical sites contiguous with that tissue. There are no reservoir hosts for this parasite. The blackfly, *Simulium spp.,* is the vector of 0. *volvulus.* This filarial parasite occurs in Africa, and throughout Latin America. Onchocerciasis used to be the major cause of blindness[1] throughout sub-Saharan Africa, often affecting more than 50% of the inhabitants of towns and villages in endemic areas. The advent of the ivermectin program, administered jointly by the World Health Organization, The Clark Foundation, and Merck & Co., has seen the incidence and prevalence of onchocerciasis reduced in Africa by more than 90% in many regions. It was once so prevalent that people could not live in many places along riverbanks. Hence, the turnabout in this disease over the last five years has been nothing short of a miracle in the annals of international public health practice.

With the intensified efforts to eradicate river blindness, public health officials have started to enter regions not previously under surveillance. It has been pointed out that because of this new intense scrutiny of the infection, there has been a paradoxical rise in the global estimates of prevalence.' Approximately 18 million people are infected with *0. volvulus,* worldwide. Nearly all of them live in Africa (with about one-half in Nigeria and Congo), with about 150,000 cases in the American tropics.' An estimated 270,000 persons have been blinded as a result of onchocerciasis, almost all of whom live in sub-Saharan Africa. Onchocerciasis is still the fourth leading cause of blindness in the world.[3] The disease also causes a disfiguring dermatitis that is second only to polio as a cause of long term disability in endemic areas.

Historical Information

Onchocerca volvulus was first described in Africa by Leuckart. He recounted his discovery of the parasite to Patrick Manson, who, in turn, published the full description in 1893, giving Leuckart full credit.' Earlier O'NeiII' observed the microfilariae of this filarial nematode in the skin of a patient from \/\'est Africa. Onchocerciasis in Latin America was not reported until 1917, when Robles" found ocular disease associated with the presence of nodules on the forehead of a small boy. He dissected the nodule and found that it contained the adult worms. Later Robles described the worm, the pathology of the disease, and epidemiology of the infection. Moreover; he suspected that the blacklly was the vector, which was proved by Blacklock' in 1927.

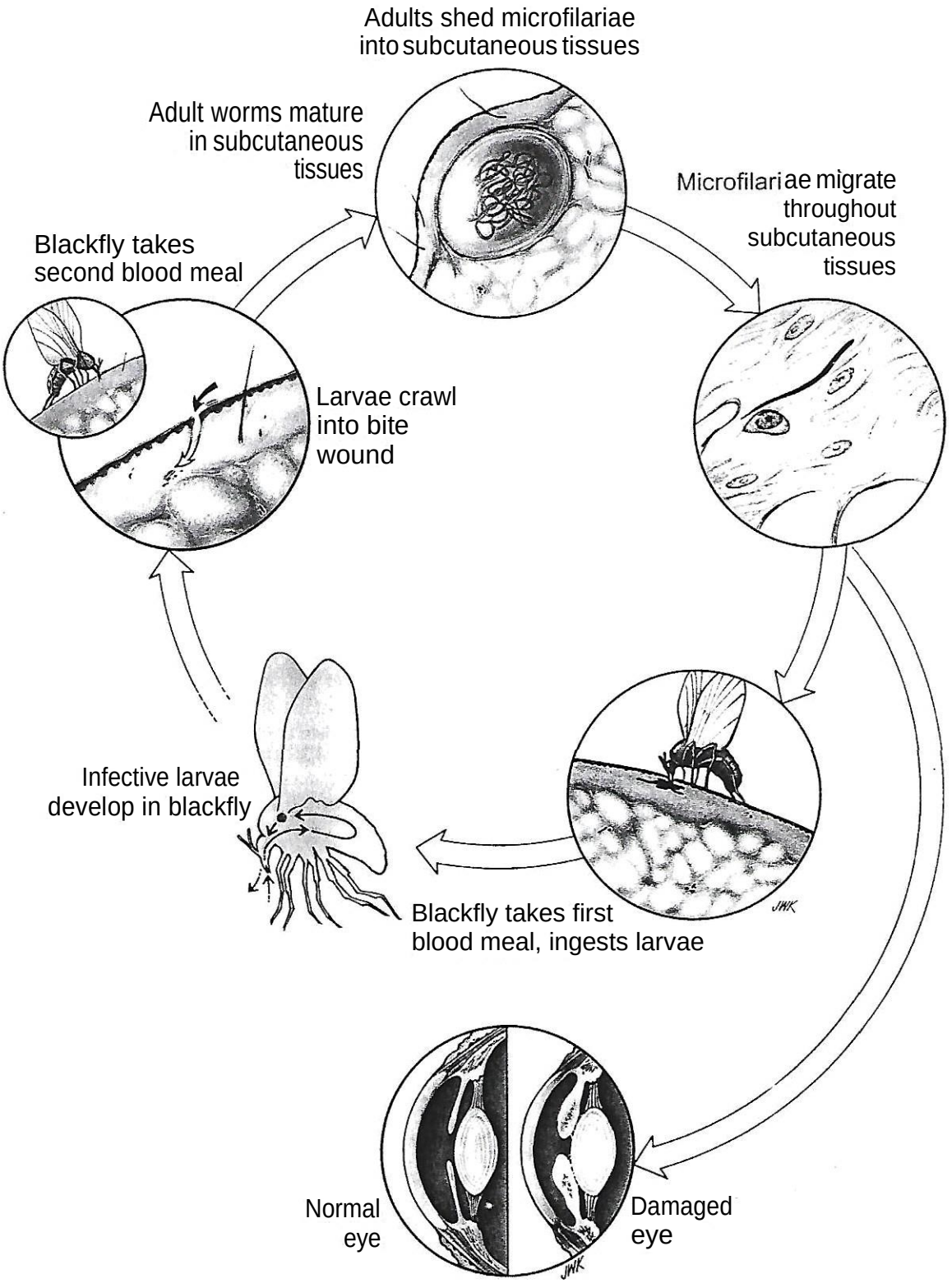
Life Cycle

Adult females measure about 40 cm in length and 0.3 cm in width, while the male measures about 3 to 5 cm in length. Both sexes lie entwined about each other, locating to subcutaneous fibrous noduies, onchocercomas (Fig. 23.1), which vary in size depending on the number of adult worms in them. Some nodules are so small that they cannot be palpated.' Microfilariae are produced within the nodules, and leave these sites to migrate throughout the subcutaneous tissues (Fig. 23.2, 23.3). The blackfly (Fig. 39.5) acquires the larvae while taking a blood meal. The immature worms penetrate the insect's hemocele, and the muscle fibers of the flight wing bundles in the thorax. After 6-8 days of development, during which the larvae molt twice, the now infective larvae leave the muscles, enter the cavity of the proboscis, and are deposited on the skin when the fly bites. *larvae* enter the dite wound *after the fly* withdraws its biting mouth parts. The immature parasites invade the subcutaneous tissues with the aid of a protease," and take up residence there. After completing their development, they mate. Adults produce hundreds to thousands of microfilar ae during their life span (about 700 microfilariae per day) of 8-10 years. Growth and molting of worms in the subcutaneous tissues induces formation of the fibrous nodules, and also elicits an angiogenic response, resulting in the production of a network of vessels, the function of which is presumably to supply nutrients to the parasites and carry away metabolic wastes. A similar angiogenic response is induced by the Nurse cell-parasite *com*plex of *Trichinella spiralis.*

Cellular and Molecular Pathogenesis

0. volvulus has impressive immuno-modulatory properties, with the capacity to bias host responses to a Th2 type pattern. By this mechanism host cell

Onchocerca volvulus



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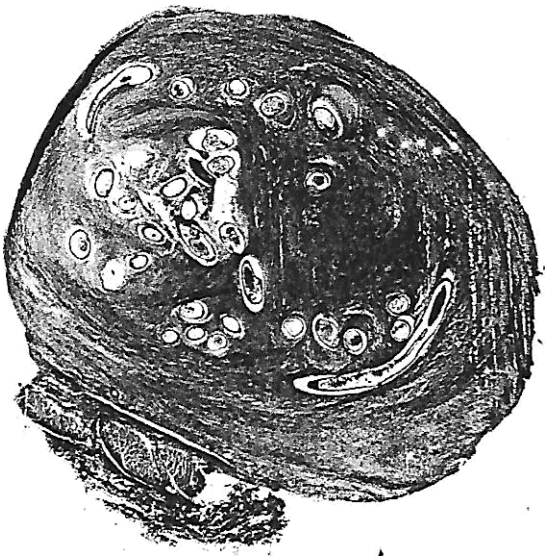


Figure 23. 1. Cross section of nodule (onchocercoma) induced by *Onchocerca volvulus.* Numerous sections of adult worms are seen. 2.5 cm in diam.

mediated Th1 type immunity is suppressed leading to impaired responses to PPD skin testing for tuberculosis,'° and even increased susceptibility to intercurrent infections with lepromatous leprosy."

The degree of pathogenesis varies directly with the intensity of infection and the degree of host responsiveness to dying adult worms and microfilariae and their secretions. Dead microfilariae induce inflammatory reactions that become more severe as the infection persists. This point is important when considering therapy. The lesions, primarily involving the skin and the eyes, occur as a consequence of cell-mediated immunity to parasite antigens. Individuals with the most vigorous cell-mediated immune responses develop the most severe manifestations.[1"' '°]

The major ocular lesions occur in the cornea to produce a keratitis. In this case the keratitis results from an accumulation of punctate opacities in the cornea that arise from a unique immunopathologic damage to microfilafiae in the eye. This is a Th2-dependent process with a heavy' reliance on host interleukin 4.'[z] In the skin, similar immune responses lead to pruritus and angioedema.

Subcutaneous nodules, the other hallmark of clinical onchocerciasis, *vary'* in size from barely *discern*able to approximately 5 cm in diameter. Nodules develop over an 18-month period depending on the number of adult worms in each. The number of nodules *a]so* varies, from an occasional one to several hundred, occupying large areas of subcutaneous tissue. In the latter instance, blackflies biting such individuals may actually expire, due to the overwhelming nature of the infection in their flight wing muscles.

Those areas in which peripheral lymphatics converge (e.g., occiput, suboccipital areas, intercostal spaces, axilla, and iliac crests) have the highest predilection for nodules. The body regions most affected differ according to geographic locales. In Africa, for example, the nodules predominate in the lower part of the body, whereas in Central America they tend to be found more often in the upper portions of the body. This difference is related to the biting habits of the vector insects, and the styles of clothing worn by the inhabitants of each endemic area.

Glinical Disease

Clinical onchocerciasis includes dermatitis, eye lesions, and onchocercomas.

Onchodermatitis.

Mild infection (less than five nodules per infected individual) is usually asymtomatic. In contrast, moderate to severe infection (ten or more nodules, with many in the head and neck region) produce correspondingly more serious and more numerous symptoms. Involvement of skin is characterized by intense itching, which is associated with a rash consisting of numerous small, circular elevated papules 1-3 mm in diameter. On white skin, the papules are reddish, but on black skin, they tend to be dark brown. The pruritus of onchodermatitis is intense and disabling. Occasional suicides result from the extreme discomfort associated with it.[1] The affected areas of skin become edematous and thickened, and it looses its elasticity. The skin can take on an orange-peel quality. Over time, the skin will atrophy, especially over the buttocks, with appearance of wrinkles. Depig-

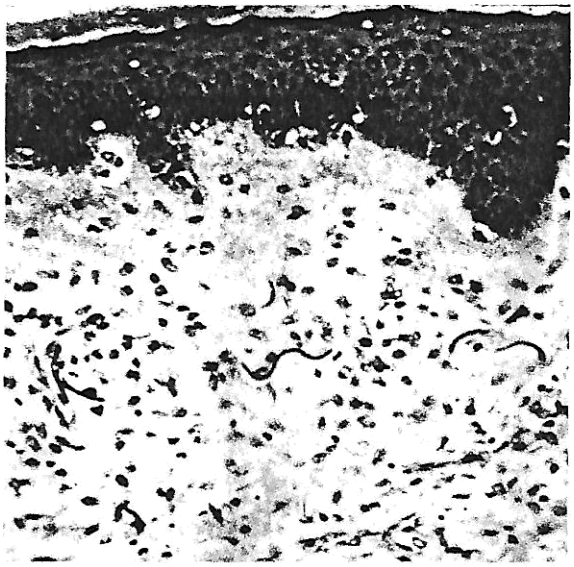


Figure 23.2. Section of skin with numerous microfilariae of *O. volvulus.*



Figure 23.3. Higher magnification of a microfilaria of *O. volvulus* in skin. 310 pin x 7 /Jm.

mentation can also occur, especially over the shins. Sometimes this is known as “leopard skin". These sequelae are more common in Africa than in Central America, but Central American children who are infected may have facial lesions, reddish in color described as erisipela de la costa.

Lymphadenopathy

Lymph node involvement in *A'irica* is usually found in the inguinal and femoral nodes, whereas in the American tropics it is in the head and neck. Advanced lymph node involvement can lead to adenocele formation.’

Ocular Lesions.

All parts of the eye are affected in chronic, long-term infections. Initially, there may be conjunctivitis, with irritation, !acrimation, and photophobia, a reaction analogous to the dermatitis in response to dead microfilariae. The cornea at this time reveals the punctate lesions of keratitis. Slit-lamp examination reveals motile or dead microfilariae in the conjunc-*tiga. A long-standing* infection produces sclerosis and vascularization. Sclerosing keratitis is the leading cause of blindness due to *onchocerciasis,* and develops over a 20- to 30-year period. Onchocercal blindness peaks in those beMeen 30 and 40 years of age; individuals most responsible for taking care of their families.’ The anterior chamber is also invaded, and microfilariae can be seen there with a slit lamp. Finally, there may be iritis, iridocyclitis, and secondary glaucoma. Invasion of the posterior segment of the eye causes optic neuritis and papillitis; the choroid and the retina are also involved.

Diagnosis

Because of its highly focal distribution, a travel history is critical in order to entertain a clinical suspicion of onchocerciasis. A definitive diagnosis is usually made by examining a piece of skin (2-5 mm*) dissected from the affected part of the body. In Africa, the specimen should be obtained from the lower part of the body, and in Central America from the upper part. The skin should be alcohol-cleansed, elevated with a needle, and cut with a scalpel blade. Next, a preferably bloodless piece should be placed in warm physiological saline and examined microscopically for motile microfilariae within 10 minutes. A representative sample of skin can be weighed and the number of microfilariae per milligram of tissue calculated as an index of the intensity of infection. In addition, the piece of skin can be pressed against a dry microscope slide, and the impression stained with Giemsa solution and examined microscopically for microfilariae (Fig. 23.4). Histologic sections of a subcutaneous nodule (Figure 23.2, 23.3.) may also reveal microfilariae. The sensitivity of skin snips has recently been improved by PCR amplification using primers that encode portions of a 150 bp repeat.’°

The Mazzotti Test is a provocative challenge test using a 50 mg dose of diethylcarbamazine (DEC). Within 3 hours after treatment, patients *with 0. volvulus* infection will develop pruritus. In heavily infected patients, the Mazzotti reaction can be severe and may exacerbate the ocular pathology in a patient. As an alternative, some physicians perform a type of patch test by applying DEC to a small region in order to elicit a local Mazzotti-like reaction.*'¹^

Serologic tests that measure lgG antibodies to 0. *volvulus* are sensitive, but their specificity is poor, and not yet useful to the clinician. Efforts are underway to develop recombinant immunodiagnostic reagents.

Treatment

Ivermectin is the drug of choice for onchocerciasis. Ivermectin inhibits the release of microfilariae from the female." Usually a single oral dose of 150 mcg/kg administered every 6 months will *slow* or reverse the progression of both ocular and cutaneous

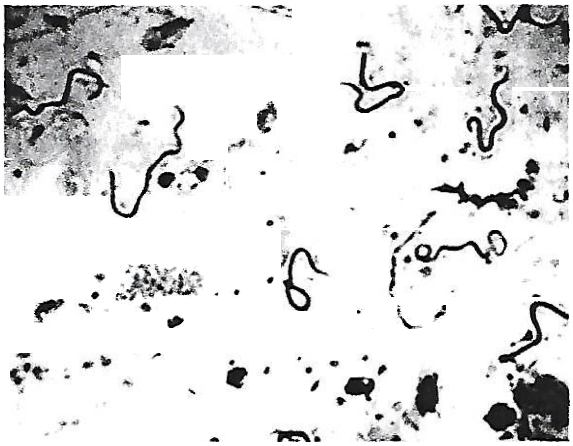


Figure 23.4. Impression smear of a skin *snip (rom a* patient heavily infected with O. *volvulus.* Microfilariae were visualized with Giemsa stain.

diseases."The drug is available through the Mectizan Donation I-'rogranJ es!ahlished in 1986 by Merck & Co. Ivermectin does not kill the adult worms encased in a nodule. Therefore, repeat dosing is necessary to suppress the release of microfilariae In some patients more frequent interval dosing is required in order to suppress pre ritus. Community-wide chemotherapy interrupts transmission of onchocerciasis."" The major toxicity of ivermectin is generally not from the drug itself but rather from its ability to increase the antigen load from dead and dying parasites, leading to fever; angioedema and pruritus. These symptoms usually occur within 24 hours of treatment. In those patients with concurrent Loa /oa infection, ivermectin can elicit severe reactions, including encephalopathy.[2'] This point is especially critical in areas such as West and Central Africa, where there is epidemiologic overlap between the two helminth infections. In Latin America, the surgical removal of palpable subcutaneous nodules has led to successful resolution of the infection in some instances.

Prevention and Control

Onchocerca volvulus distribution follows that of the dipteran vectors. Blackflies breed in fast-running water of mountainous streams in regions of Africa and South and Central America, and they have a fairly long flight range. Thus, onchocerciasis can be found several miles from the nearest endemic breeding site. Because much of the coffee of the world is grown on mountainous hillsides, the prevalence of onchocerciasis among workers on coffee *plantations* is high. Control of the disease should first employ the use of ivermectin to reduce microfiTarial worm burdens in infected people. By 1995, over 9 million ivermectin doses per year were being distributed.[2]

Reducing larval vector populations using DDT and other insecticides in streams and rivers has also been tried, with variable success. Because all species of macroinvertebrates in the treaded rivers are affected by these agents, severe, adverse effects on food chains and food webs have often resulted. Significant reductions in the incidence of onchocerciasis has resulted in the resurgence of blackflies in some regions. In these cases, insecticide use has been reinstated. Unfortunately, and quite predictably, blackflies in many areas have developed resistance to a wide variety of insecticides.

A multidisciplinary program was 'vitiated by the WorJd Health Organization in seven African nations (Benin, Burkina Faso, Cote d'Ivoire, Ghana, Mali, Niger and Togo), covering almost 1 million square kilometers of land, to serve as a model for control programs of onchocerciasis. The onchocerciasis control program incorporates elements of vector control, chemotherapy with ivermectin treatment and surveillance. The control program in Africa will run through *20D7. So* far; Merck and Co. has committed over 400 million ivermectin tablets valued at over $200 million.'

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24. 1oa *loa* (Cobbold 1864)

Introduction

Loa /oa is a member of the filarial group of nematodes, and its distribution is limited to Central ard West Africa, where it infects up to 13 million individuals. In some hypereridemic regions, up to 40% of a population may be clinically infected.' Loiasis is an emerging infection in areas where the establishment of rubber plantations has altered the rain forest ecology.* Adult worms live in subcutaneous tissues. Their main vectors are dipteran flies of the genus Chrysops. Loa *loa* has no reservoir hosts.

Historical Information

Argyll-Robertson, in 1895,° gave the first complete description of the worm and the clinical presentation of the infection. The woman from whom he removed two adult worms (one of each sex) had lived in West Africa in Old Calabar Swellings in her arms accompanied her infection and were described in detail. These inflammatory lesions are still referred to as Calabar swellings. Leiper, in 1913,‘ described two species of dipterans, *Chrysops dimidiata* and *C. silacae.* as the vectors of L. *loa.*

Life Cycle

Female adults measure 0.5 mm wide and 60 mm long; the males are 0.4 mm by 32 mm. Adult worms deposit microfilariae (Fig. 24.1), while they wander throughout the subcutaneous tissues. Microfilariae (80 pm long by 7 pm in diameter) penetrate capillaries and enter the bloodstream, where they circulate until they beame ingested in a blood meal by a mango fly *(Chrysops spp.). L. loa* microfilariae exhibit diurnal periodicity that coincides with the feeding habits of Chrysops.° Larvae penetrate the stomach of the fly, and *locate* to the faf body. Eight to ten days later the infective third-stage larvae migrate to the cavily of the biting mouth parts, and are released into the bite wound when the fly takes another blood meal. The larvae, now in the subcutaneous tissues of the host, develop slowly into adults within 1-4 years. The adult worms can live in the tissues for up to 17 years.° Mature worms mate, and the females begin depositing microfilariae. The nutñtional requirements of L. /oa are unknown.

Cellular and Molecular Pathogenesis

Neither the adult wnrrns in the subcutaneous tissues of th•. hcst nor the microfilariae in it.e bloodstream cause any direct pathologic changes. However in some individuals the parasite can elicit a number of immune-mediated responses that have an allergic basis. There appear to be at least three major groups of individuals who experience different immunopathological responses to the parasle. One of these groups is comprised of asymptomatic individuals who have diminished anti-Loa allergic responses. These groups typically have high levels of circulating microfilariae. The second group is typified by individuals who develop pronounced immunopathology with characteristic recurrent angioedema and Calabrar swellings.’ These individuals develop Calabar swellings as a local inflammatory reaction that may precede the migrating adult worms. It is presumed to result from vigorous host IgE responses and interleukin-5 production in response to adult worm secretions, or even microfilarial antigen released by female worms. Host IL-5 production results in circulating eosinophilia.^"The Calabar swellings are typically more severe in visitors to endemic areas than in residents who live for many years in these same regions.*"“ There is still a third group of individuals who neither have circulating microfilariae nor Calabar swellings. These are individuals who live in hyperendemic areas yet are believed to have developed protective immunity“"“

Clinical Disease

Calabar swellings are 10-20 cm non-erythematous angioedematous swellings that last for a few days. They occur most typically on the extremities and the face, particularly in the periorbital region.



Figure 24.1. Microfilaria of *Loa loa.* 240 pm

The angioedema is often preceded by pain and itching. Recurrences are common. The occasional passage of an adult worm across the subconjunctival space of the eye is perhaps more disturbing to most infected persons. F'atients with more serious complications, including cardiomyopathy, nephropathy, and pleural effusions, have been reported.'[1] Some complications occur only after administration of diethylcarbamazine. These sequelae may result from immune complex deposition. Encephalitis has also been described in patients with very high levels of microfilariae, including microfilariae in the cerebrospinal fluid.'* Most of these patients have received diethyl-carbamazine and probably occurs as part of the host immune response in the central nervous system. A rare cardiac condition known as endomyocardial fibrosis may result from eosinophilic infiltration of the myocardium in response to L. /oa.[1']

Significant differences in the clinical presentation of loiasis occur among long-term visitors to endemic areas, in contrast to people native to these areas.° People living in endemic regions are asymptomatic, despite high levels of microfilaremia, whereas visitors and expatriates suffer from a variety of allergic responses, such as frequent episodes of ar.gioedema, Calabar swellings, hypereosinophilia, and hyper-gammaglobulinemia. This disorder is sometimes referred to as the "hyper-responsive syndrome" of loiasis, reflecting elevated humoral and cell-mediated immune responses to the parasite.[11]

Diagnosis

Patients returning from West or Central Africa with localized angioedema or a worm beneath the conjunctiva should be suspected of having loaiasis. The Calabar swellings should be clinically differentiated from other causes of angioedema, including C1 inhibitor deficiency.[1"] Definitive diagnosis is by identifying the microfilariae microscopically in a thin blood smear stained with either Giemsa or Wright's solution. Among the distinguishing features of *L.* /oa microfilariae (Fig. D.54 and D.55, Appendix D) are their diurnal periodicity, the presence of a sheath, and three or more terminal nuclei." Adult worm can be recovered from the sub-conjunctival space, and various subcutaneous tissues. There are serologic tests available but largely on a research basis. Anti-Loa antibodies of the IgG4 immunoglobulin subclass are a reliable marker of active infection.[1'] However testing is limited to a few laboratories that have access to *L. loa* antigen prepared from the worms. There is also a PCR based assay that has been developed to detect microfilarial genomes in blood.[1°]

Treatment

Diethyl-carbamazine (DEC) at a dose of 8-10 mg/kg/day for 21 days is the drug of choice for loiasis. The drug destroys both adult worms and microfilariae. The full dose of the drug is not typically started on the first day of treatment. Instead, it is given in a graded manner; beginning with a test dose on day 1 of 1 mg/kg p.c., followed by 1 mg/kg tid on day 2, and 1-2 mig/kg tid on day 3. This is done to reduce the likelihood of treatment-associated sequelae including encephalitis.""It has been suggested that concerns about iatrogenic complications of loiasis increase when the microfilarial concentration in blood exceeds 2500 mf/ml.'° In very heavy infections, apheresis has been reported to effectively lower microfilarial counts prior to definitive treatment.[1^] Albendazole and ivermectin have also been used to reduce microfilaremia in this manner.'° Antihistamines or corticosteroids may be required to decrease allergic reactions during treatment. In up to 50% of patients, DEC treatment may need to be repeated several times in order to effect a cure. Adult worms in the eye must be removed surgically. Weekly chemoprophylaxis with DEC given in a dose of 300 mg is effective in preventing loiasis among long-term visitors."

Prevention and Control

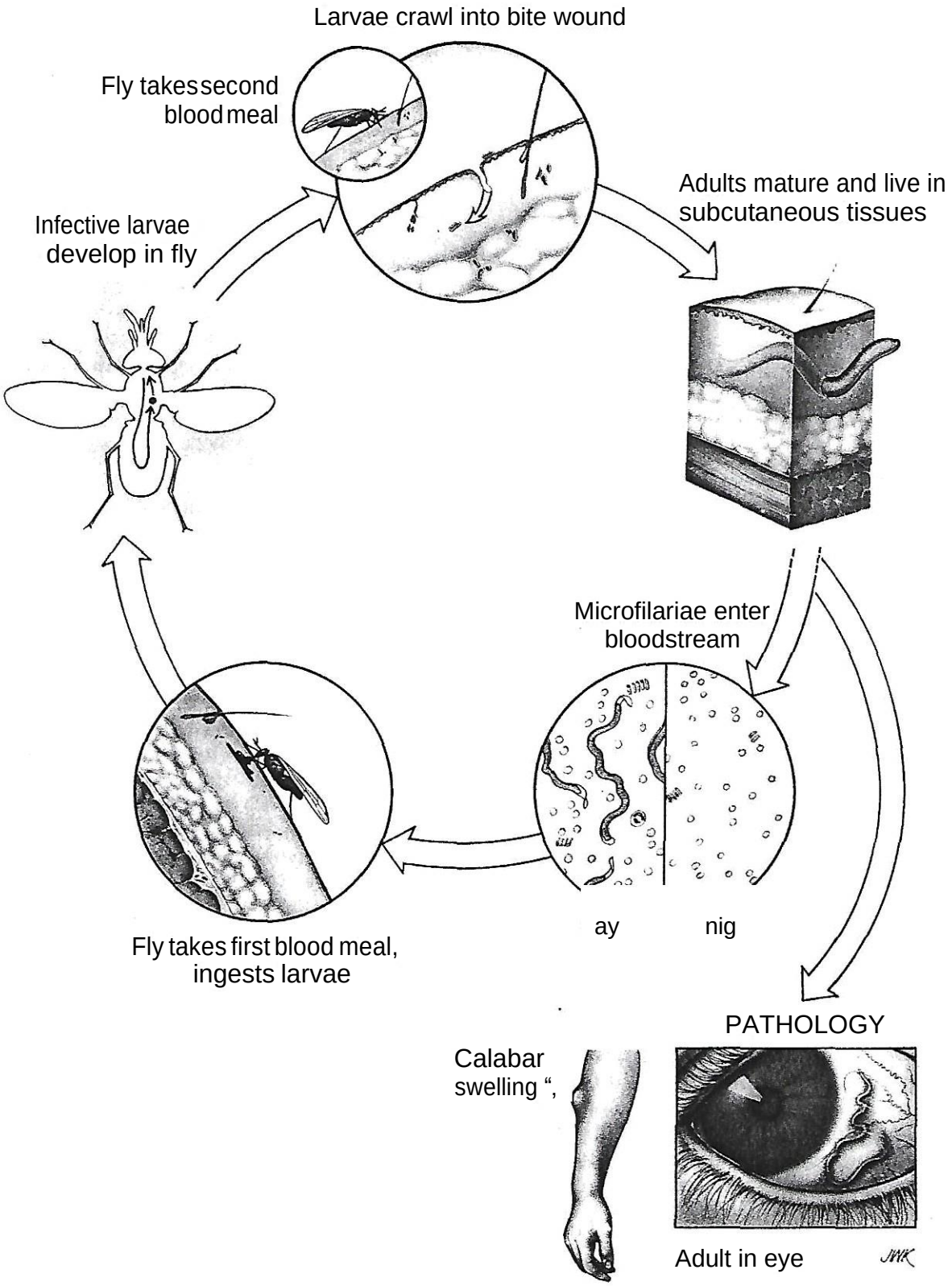
In hyperendemic regions of central Africa, 95% of the population have antibodies to L. *loa* antigen by the age of two years.[21] In the Chailu Mountains in Zaire, 19% of the native populations are microfilaremic, and more than 50% of the adults have reported subconjunctival migrations of an adult worm. Mass or targeted chemotherapy with ivermectin may reduce transmission in these areas.*[1]

Spraying mango groves with insecticides, particularly DDT, remains an effective method for controlling populations of the vector since resistance to this insecticide in Chrysops has not yet developed.

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Loa loa



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OPEN

Citation: Blood Cancer Journal (2016) 6, e441; doi:10.1038/bcj.2016.50

www.nature.com/bcj

REVIEW

'Acute myeloid leukemia: a comprehensive review and 2016 update'

I De Kouchkovsky[1] and M Abdul-Hay[1,2]

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, with an incidence of over 20 000 cases per year in the United States alone. Large chromosomal translocations as well as mutations in the genes involved in hematopoietic proliferation and differentiation result in the accumulation of poorly differentiated myeloid cells. AML is a highly heterogeneous disease; although cases can be stratified into favorable, intermediate and adverse-risk groups based on their cytogenetic profile, prognosis within these categories varies widely. The identification of recurrent genetic mutations, such as FLT3-ITD, NMP1 and CEBPA, has helped refine individual prognosis and guide management. Despite advances in supportive care, the backbone of therapy remains a combination of cytarabine- and anthracycline-based regimens with allogeneic stem cell transplantation for eligible candidates. Elderly patients are often unable to tolerate such regimens, and carry a particularly poor prognosis. Here, we review the major recent advances in the treatment of AML.

Blood Cancer Journal (2016) 6, e441; doi:10.1038/bcj.2016.50; published online 1 July 2016

INTRODUCTION

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, accounting for ~80 percent of cases in this group.[1] Within the United States, the incidence of AML ranges from three to five cases per 100 000 population. In 2015 alone, an estimated 20 830 new cases were diagnosed, and over 10 000 patients died from this disease.[2] The incidence of AML increases with age, from ~1.3 per 100 000 population in patients less than 65 years old, to 12.2 cases per 100 000 population in those over 65 years. Although advances in the treatment of AML have led to significant improvements in outcomes for younger patients, prognosis in the elderly who account for the majority of new cases remains poor.[3] Even with current treatments, as much as 70% of patients 65 years or older will die of their disease within 1 year of diagnosis.[4]

PATHOPHYSIOLOGY

AML can arise in patients with an underlying hematological disorder, or as a consequence of prior therapy (for example, exposure to topoisomerases II, alkylating agents or radiation).[5] However in majority of cases, it appears as a *de novo* malignancy in previously healthy individuals. Regardless of its etiology, the pathogenesis of AML involves the abnormal proliferation and differentiation of a clonal population of myeloid stem cells. Well-characterized chromosomal translocations, such as t(8:21) in core-binding factor AML (CBF-AML) or t(15:17) in acute promyelocytic leukemia (APL) result in the formation of chimeric proteins (RUNX1-RUNX1T1 and PML-RARA, respectively), which alter the normal maturation process of myeloid precursor cells. In addition to large chromosomal rearrangements, molecular changes have also been implicated in the development of AML. In fact, genetic mutations are identified in more than 97% of cases,[6] often in the absence of any large chromosomal abnormality.[7] Studies of animal models at the turn of the century led to the development of a two-hit model of leukemogenesis, which offers a conceptual framework for classifying the various mutations associated with AML.[8] According to this model, class I mutations which result in the activation of pro-proliferative pathways must occur in conjunction with class II mutations which impair normal hematopoietic differentiation in order for leukemia to develop.[9,10] Common class I mutations, such as FLT3 (internal tandem duplications, ITD, and tyrosine kinase domain mutations, TKD), K/NRAS, TP53 and c-KIT are found in ~28, 12, 8 and 4% of cases, respectively.[7] Studies of solid and hematological malignancies have also highlighted the role of signal transducer and activator of transcription 3 (STAT3) in the stimulation of cellular proliferation and survival.[11–13] Enhanced tyrosine phosphorylation of STAT3 whether due to increased secretion of cytokines, such as IL-6(ref. 14) or mutations in receptor tyrosine kinases (for example, FLT3 duplications[15] or less frequently JAK2)[16] is seen in up to 50% of AML cases and signifies a worse prognosis. Notable class II mutations include NPM1 and CEBPA, which are found in ~27% and 6% of cases, respectively, and confer a better prognosis.[7] Alterations in genes involved in epigenetic regulation have recently emerged as a third class of mutations, with downstream effects on both cellular differentiation and proliferation. These include mutations in the DNA-methylation related genes DNMT3A, TET2, and IDH-1 and IDH-2,[6,7] which are found in more than 40% of AML cases.

Despite significant advances, much remains to be discovered on the exact contribution of these individual mutations to the development of AML. As suggested by the 'two-hit model,' the pathogenesis and behavior of AML depends heavily on the interactions between different somatic alterations and chromosomal rearrangements. Thus, the c-KIT mutation has been

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Received 13 April 2016; revised 3 May 2016; accepted 19 May 2016

associated with t(8;21) or inv(16), and its presence carries significant implications regarding prognosis. Similarly, NMP1 (a class II mutation) frequently occurs in conjunction with the class I mutation FLT3-ITD, or mutations in the epigenetic genes DNMT3A and IDH-1 or IDH-2.[6]

Most of the clinical manifestations of AML reflect the accumulation of malignant, poorly differentiated myeloid cells within the bone marrow, peripheral blood and infrequently in other organs. The majority of patients presents with a combination of leukocytosis and signs of bone marrow failure such as anemia and thrombocytopenia. Fatigue, anorexia and weight loss are common complaints; lymphadenopathy and organomegaly are not typically seen. If left untreated, death usually ensues within months of diagnosis secondary to infection or bleeding. The diagnosis of acute leukemia is established by the presence of 20% or more blasts in the bone marrow or peripheral blood.[17] AML is further diagnosed by demonstrating the myeloid origin of these cells through testing for myeloperoxidase activity, immunophenotyping or documenting the presence of Auer rods. The latter finding consists of azurophilic, often needle-shaped cytoplasmic inclusion bodies that are commonly seen in APL, acute myelomonocytic leukemia and the majority of AML with t(8;21). The diagnosis of AML can also be established in the presence of an extramedullary tissue infiltrate, or a documented t(8;21), inv(16) or t(15;17) in the appropriate clinical setting, regardless of the blast percentage.[18]

CLASSIFICATION

The French–American–British classification system represents the first attempt to distinguish between different types of AML. Established in 1976, it defines eight subtypes (M0 through M7) based on the morphological and cyto-chemical characteristics of the leukemic cells. In 2001, as part of an effort to integrate advances made in the diagnosis and management of AML, the World Health Organization (WHO) introduced a new classification system followed by a revised version in 2008.[18] Later in 2016 a new revised version was released, the WHO classification of AML distinguishes itself by incorporating genetic information with morphology, immunophenotype and clinical presentation to define six major disease entities: AML with recurrent genetic abnormalities; AML with myelodysplasia-related features; therapy-related AML; AML not otherwise specified; myeloid sarcoma; and myeloid proliferation related to Down syndrome (Table 1).[19] Among cases of AML with recurrent genetic abnormalities, 11 subtypes are further delineated according to distinct chromosomal translocations. In addition, the provisional entities AML with mutated NPM1 and AML with mutated CEBPA were introduced as part of the 2008 revision,[18] while AML with BCR-ABL1 and AML with mutated RUNX1 were introduced as part of the 2016 revision.[19] Genetic abnormalities also inform the diagnosis of AML with myelodysplasia-related changes: along with a history of MDS or morphological evidence of dysplasia in two or more myeloid cell lineages, the presence of myelodysplasia-related cytogenetic abnormalities such as monosomy 5 or 7, and deletion 5q or 7q identify cases of AML with myelodysplasia-related features.

PROGNOSTIC FACTORS

Accurate assessment of prognosis is central to the management of AML. By stratifying patients according to their risk of treatment resistance or treatment-related mortality (TRM), prognostic factors help guide the physician in deciding between standard or increased treatment intensity, consolidation chemotherapy or allogenic hematopoietic stem cell transplant, or more fundamentally in choosing between established or investigational therapies. Among clinical factors, increased age and poor performance status are both associated with lower rates of complete remission (CR) and decreased overall survival (OS).[3,20] Age and performance status at diagnosis similarly help to predict the risk of TRM, although multivariate model analyses suggest that other variables such as platelet count, serum creatinine or albumin rather than age itself account for most of the increased risk of TRM seen in older patients.[21] Therapy-related AML and AML associated with a prior hematological malignancy also carry a significantly poorer prognosis.[22] Although clinical factors have an important role in

Table 1. WHO classification of AML and related neoplasms

Types	*Genetic abnormalites*
AML with recurrent genetic abnormalities	AML with t(8:21)(q22;q22); RUNX1-RUNX1T1
	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	APL with PML-RARA
	AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	ML with t(6;9)(p23;q34.1); DEK-NUP214
	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
	AML (megakaryoblastic) with t(1;22)(p13.3;q13.3); RBM15-MKL1
	AML with BCR-ABL1 (provisional entity)
	AML with mutated NPM1
	AML with biallelic mutations of CEBPA
	AML with mutated RUNX1 (provisional entity)
AML with myelodysplasia-related changes	
Therapy-related myeloid neoplasms	
	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/monocytic leukemia
	Acute erythroid leukemia
	Pure erythroid leukemia
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis
Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	Transient abnormal myelopoiesis
	ML associated with Down syndrome

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ML, myeloid leukemia; WHO, World Health Organization.

guiding therapy, cytogenetic changes constitute the single strongest prognostic factor for CR and OS in AML. Accordingly, cases of AML can be stratified into favorable, intermediate or adverse prognostic risk groups based on their cytogenetic profile alone. The chromosomal rearrangements t(8;21), t(15;17) or inv(16) all confer a favorable prognosis,[17,23] with a 3 year OS of 66% and 33% in patients younger and older than 60 years, respectively.[24] In contrast, cytogenetic changes such as a complex karyotype (that is, three or more chromosomal abnormalities in the absence of any of the recurrent genetic abnormalities identified in the WHO 2008 classification), monosomy 5 or 7, t(6;9), inv(3) or 11q changes other than t(9;11) have all been associated with a significantly higher risk of treatment failure and death (Table 2).[24] AML cases with an intermediate prognostic risk mainly constitute of patients with normal cytogenetics (CN-AML).[17,24]

Gene mutations have helped further refine risk stratification based on cytogenetic changes alone. Among patients with t(8;21), the presence of a c-KIT mutation significantly increases the risk of relapse, and decreases OS to levels comparable to those of patient with intermediate-risk AML.[6,23,25] Although there is some evidence that the presence of c-KIT mutations similarly lowers prognosis in patients with inv(16),[26] recent studies have failed to show any prognostic impact in this subset of cases.[6,27,28] Molecular changes have a particularly important role in refining the prognosis of patients with CN-AML, which includes nearly half of *de novo* AML cases. Thus CN-AML with a mutated CEBPA or a mutated NPM1 in the absence of FLT3-ITD has been identified as having a prognostic risk similar to that of AML with favorable cytogenetic changes.[17,29] The favorable prognostic impact of CEBPA mutations has been further refined to biallelic mutations only.[30] On the other hand, multiple studies[29,31] including a meta-analysis of relapse-free survival (RFS) and OS in patients with CN-AML o60 years of age have consistently shown the presence of FLT3-ITD to be associated with a worsened prognosis.[6,32] This has led to the classification of CN-AML with FLT3-ITD into the adverse prognostic-risk group.[23,33] As with CEBPA mutations, the prognostic impact of FLT3-ITD may depend on the presence of biallelic mutations. Several studies have shown a significantly worse prognosis in patients with higher mutant to wild-type allelic ratios.[34,35] TP53 mutations, which are found in only 2– 8% of cases,[6,7] occur more frequently in cases with unfavorable cytogenetic and a complex karyotype.[36] However regardless of the cytogenetic profile, TP53 mutations are associated with a very poor prognosis[10] and may in fact represent the single worst genetic prognostic factor.[36] Mutations in DNA-related genes also carry important implications for the prognosis and treatment of AML. The presence of a mutated DNA methyl transferase gene *DNMT3A* has been associated with a worsened prognosis in CN-AML and adverse-risk AML.[37] Partial tandem duplications of KMT2A (previously known as MLL), which encodes a histone methyltransferase, have also been associated with a worse prognosis in CN-AML.[6,10,36] The prognostic impact of IDH-1/IDH-2 mutations is less well established and is likely modified by co-occurring mutations. Among cases of FLT3-ITD-negative and NPM1-mutated CN-AML, IDH-1/IDH-2 mutations have been shown to improve OS.[6] However a recent study of 826 patients with known IDH-1 and IDH-2 status found no prognostic impact on treatment response or OS.[38] Further analysis is required to delineate the role of DNA-related genes in OS and treatment response. In addition to genetic profiling at the time of diagnosis, information gained after treatment initiation plays a growing role in refining patient prognosis: As could be expected, individuals who achieve CR (defined morphologically as a blast count of o5% of total nonerythroid cells in the bone marrow) after induction therapy have a significantly increased survival compared with patients with treatment resistant AML.[39,40] Survival among patients achieving CR is further influenced by the correction or persistence of thrombocytopenia, with a shorter duration of survival observed in the latter group.[40] More recently, techniques such as real-time PCR and flow cytometry have been used to measure the presence of minimal residual disease among patients in CR. Persistently elevated levels of RUNX1-RUNX1T1 transcripts after induction therapy in patients with t(8;21) AML are thus associated with an increased incidence of relapse.[41,42] Similarly among patients with intermediate-risk disease, detection of minimal residual disease by flow cytometry is an independent predictor of relapse and survival[43,44] and carries important implications for management.[45]

ESTABLISHED TREATMENTS

Eligible patients first undergo induction therapy to achieve CR. Unfortunately, minimal residual disease often persists in CR, and

Table 2. Prognostic-risk group based on cytogenetic and molecular profile

Prognostic-risk group	*Cytogenetic profile alone*	*Cytogenetic profile and molecular abnormalities*
Favorable	t(8:21)(q22;q22) inv(16)(p13;1q22) t(15;17)(q22;q12)	t(8:21)(q22;q22) with no c-KIT mutation inv(16)(p13;1q22) t(15;17)(q22;q12) Mutated NPM1 without FLT3-ITD (CN-AML) Mutated biallelic CEBPA (CN-AML)
Intermediate	CN-AML t(9;11)(p22;q23) Cytogenetic abnormalities not included in the favorable or adverse prognostic risk groups	t(8:21)(q22;q22) with mutated c-KIT CN-AML other than those included in the favorable or adverse prognostic group t(9;11)(p22;q23) Cytogenetic abnormalities not included in the favorable or adverse prognostic risk groups
Adverse	inv(3)(q21q26.2) t(6;9)(p23;q34) 11q abnormalities other than t(9;11) − 5 or del(5q) − 7 Complex karyotype	TP53 mutation, regardless of cytogenetic profile CN with FLT3-ITD CN with DNMT3A CN with KMT2A-PTD inv(3)(q21q26.2) t(6;9)(p23;q34) 11q abnormalities other than t(9;11) − 5 or del(5q) − 7 Complex karyotype

Abbreviations: AML, acute myeloid leukemia; ITD, internal tandem duplications.

relapse will inevitably occur if treatment is discontinued. Therefore, a favorable response to induction therapy should be followed by consolidation therapy in order to eradicate any residual disease and achieve lasting remission. The mainstay of induction therapy consists of the '7+3' regimen, which combines 7 days of continuous infusion cytarabine with 3 days of anthracycline. It is generally offered to patients with an intermediate to favorable prognosis and a low risk of TRM (for example, younger patients with good performance status, normal creatinine, albumin and platelet count).[23] Studies of induction regimens using either daunorubicin at 60 or 90 mg/m^2, or idarubicin at 12 mg/m^2 have shown similar rates of CR and survival.[23,46,47] A subset of patients with DNMT3A and KMT2A mutations, which represents a poor prognostic marker, may however benefit from higher doses of daunorubicin.[6] Standard dosing of cytarabine consists of 100–200 mg/m^2 daily administered as a continuous infusion over 7 days. Although studies have shown greater efficacy at higher doses, this added benefit is small and accrued at the cost of increased toxicity;[23,48,49] induction therapy with high-dose cytarabine is generally reserved for refractory disease. The combination of fludarabine, cytarabine, G-CSF and idarubicin (FLAG-IDA), which was traditionally used for the treatment of relapse, has also been shown to be a reasonable alternative to standard induction regimens and results in similar CR rates and OS overall but higher rates of CR after a single course.[50]

An optimal approach to elderly patients with AML has not been established. Individuals over the age of 65 are more likely to present with an adverse cytogenetic-risk profile, are less likely to respond to chemotherapy and are often more susceptible to treatment-related toxicities. However despite a significantly worse prognosis, induction therapy improves survival in patients over the age of 65 when compared with supportive care and palliative chemotherapy,[51] and should be pursued whenever possible. Hypomethylating agents, traditionally used for the treatment of myelodysplastic syndrome (MDS), have also shown efficacy in elderly patients with AML. Evidence of a therapeutic benefit was first demonstrated in *post hoc* analyses of patients with MDS who were retrospectively found to meet diagnostic criteria for AML under the WHO classification.[52] A 2012 randomized trial of the hypomethylating agent decitabine versus supportive care or low-dose cytarabine in patients 65 years or older showed a significant improvement in OS with hypomethylating therapy (although this survival advantage failed to meet statistical significance in the primary analysis).[53] A more recent trial comparing the hypomethylating agent azacitidine to supportive care, low-dose cytarabine or standard induction therapy in patients 65 years or older did not show any significant improvement in median OS.[54] However among patients pre-selected to receive supportive care, a subgroup analysis suggested a benefit to azacitidine therapy. A similar benefit was seen among patients with adverse cytogenetic-risk profile or MDR-AML.[54] These results suggest a promising role for the use of hypomethylating agents in older individuals, including as a bridge for induction chemotherapy with the goal of achieving CR.

Response to induction therapy should be evaluated 14 days after initiation of treatment with a bone marrow aspirate and core biopsy.[17] Up to 25–50% of patients show persistent cytological evidence of disease after one cycle of standard induction therapy and require reinduction.[55] Treatment options for such patients (as well as patients with a disease relapse) include a second cycle of standard dose cytarabine combined with an anthracycline, high-dose cytarabine alone or FLAG-IDA, with roughly similar CR rates of up to 50%.[23,56,57] In addition, mitoxantrone-based regimens (in combination with etoposide and/or cytarabine) have been shown to achieve CR up to 40–60% of patients with recurrent or refractory AML.[58,59] Ultimately, around 60–80% of patients with *de novo* AML will achieve CR with induction therapy.[60] Patients in remission should be offered consolidation therapy to eradicate residual disease and prevent relapse. Available options for consolidation include chemotherapy and allogeneic hematopoietic stem cell transplant (allo-HSCT). When choosing between these different options, the risk of TRM should be weighted against the risk of treatment failure or relapse. Intention-to-treat analyses (allocating patients to allo-HSCT or chemotherapy based on the availability of a related-donor) have found no benefit to allo-HSCT when compared with chemotherapy in patients with cytogenetically favorable AML in first CR.[61,62] Thus chemotherapy is a reasonable first-line consolidation choice for patients with a favorable prognosis. Regimens generally consist of intermediate-dose cytarabine (two to four cycles each consisting of six doses at 1.5–3 g/m^2), which has been shown to be as effective as high-dose cytarabine[48,50,63] or multi-agent regimens.[50] The optimal choice of consolidation therapy for patients with an intermediate-risk cytogenetic profile but favorable genetic mutations is more controversial: several studies have found no benefit to transplantation in patients with NPM1-mutated, FLT3-ITD-negative CN-AML.[64,65] However in a recent intention-to-treat analysis, allo-HSCT was shown to improve RFS in this subset of patients.[66] While these conflicting results may reflect differences in study design, the difference in observed outcomes may also reflect the modulating effect of co-occurring mutations, such as IDH-1/-2.[6] On the other hand allo-HSCT significantly prolongs RFS and OS in some patients with intermediate-risk and in most with adverse-risk AML, and should be offered as a first-line consolidation therapy in eligible patients.[62,67–69] In addition, allo-HSCT has been shown to prolong RFS and improve OS in patients with CN-AML and a high FLT3-ITD allelic ratio.[70]

NOVEL AGENTS

FLT3-ITD inhibitors

Inhibition of tyrosine kinase (TK) receptors has been used successfully in various solid and hematological malignancies, including Philadelphia-chromosome positive leukemias. Given the prognostic impact and the high rate of FLT3 mutations, inhibition of this TK has long been recognized as a potential therapeutic target in AML. Tested agents include the first-generation inhibitors sorafenib and midostaurin, as well as newer second-generation agents such as quizartinib and crenolanib.

Sorafenib. Sorafenib is a tyrosine kinase inhibitors (TKI) of RAF kinase, c-KIT, VGFR, PGFR and FLT3-ITD, which was first used for the treatment of hepatocellular and renal cell carcinoma. As early as 2008, phase I trials of sorafenib administered as a single agent n patients with FLT3-ITD-positive relapsed or refractory (r/r) AML demonstrated significant reductions in the number of leukemic cells both in the peripheral blood and bone marrow, achieving CR in several patients.[71–74] In a phase II trial of 13 patients with r/r FLT3-ITD-positive AML, single-agent sorafenib at doses of 200–400 mg twice daily established CR (including CR with insufficient hematologic recovery) in over 90% of cases. The agent was well-tolerated, with grades 3 to 4 adverse events consisting of hyperbilirubinemia (in 4/13 patients), elevated transaminases (5/13), diarrhea (4/13), rash (2/13), pancreatitis (1/13), colitis (1/13), pericarditis (1/13), hand and foot syndrome (2/13) and elevated creatinine (1/13). Yet despite a strong initial response, the majority of patients relapsed within 72 days of remission. Treatment failure was associated with the emergence of D835Y and D835H mutations within the FLT3 TKD. The addition of sorafenib to standard induction regimens has yielded similarly mixed results: although initial phases I and II trials of combination therapy were able to achieve longer periods of disease-free survival, relapse invariably ensued within several months of treatment.[75–77] In one such study, the combination of sorafenib with cytarabine and idarubicin as induction and consolidation therapy was able to achieve CR (or CR with an incomplete platelet recovery) in 18 out of 18 patients with previously

untreated FLT3-ITD-positive AML.[75] However after a median follow-up of 9 months, more than half of these patients had relapsed. Interestingly, no new mutation was observed in the FLT3 TKD of the relapsed samples available for genetic sequencing. Alternative mechanisms of resistance, such as the increased levels of FLT3 receptor ligand seen in patients receiving standard chemotherapy, have been postulated to contribute to treatment failure.[78] Combinations of sorafenib and hypomethylating agents, which have not been associated with an increase in FLT3 receptor ligand levels, are currently being investigated. An encouraging phase II trial of sorafenib and azacitidine in 43 patients with relapsed/refractory AML reported a response rate of 46%, including 16% CR and 27% CR with incomplete count recovery.[79]

The role of sorafenib as a first-line therapy in AML was further delineated in two recent randomized trials: In 2013, Serve *et al.* published the results of study, in which 201 patients 60 years or older with newly diagnosed AML were randomized to receive sorafenib or placebo in addition to standard chemotherapy. Even within the subset of patients with FLT3-ITD-positive disease, the addition of sorafenib did not result in an improved EFS or OS, and was instead associated with an increased incidence of adverse events.[80] Most recently, Rollig *et al.*[81] investigated the combination of sorafenib with standard chemotherapy in a multicenter randomized controlled phase II trial of 267 patients age 60 or younger with newly diagnosed AML. In this study, patients were randomly assigned to receive two cycles of standard '7+3' induction therapy followed by three cycles of high-dose cytarabine as consolidation therapy in combination with either sorafenib (400 mg twice daily) or placebo. Patients assigned to the sorafenib group also received 12 months of sorafenib maintenance therapy after their last consolidation cycle. After 3 years the primary end point, event-free survival, was achieved in 40% of patients in the sorafenib group, versus 20% in the placebo group (with an unadjusted hazard ratio of 0.64).[81] The occurrence of grades 3–5 diarrhea, rash, fever and bleeding were significantly increased among patients receiving sorafenib (occurring in 11, 7, 54 and 7%, respectively). Importantly, only 17% of the individuals enrolled in this study were positive for the FLT3-ITD mutation. The observed benefit in FLT3-ITD-negative AML may in part be explained by off-target inhibition of other tyrosine kinases, such as c-KIT, PGFR and RAF kinase. Alternatively as suggested by the observed increased in FLT3 receptor ligands level activation of wild-type FLT3 TK may become a driver of leukemogenesis in patients receiving standard chemotherapy.[82] By targeting FLT3 TK in the period immediately after cytarabine or daunorubicin therapy, sorafenib may exert significant anti-leukemic activity even in FLT3-ITD-negative cells.

In an interesting parallel to the use of TKI in Philadelphia-chromosome-positive leukemias, inhibition of FLT3 TK has also shown a promising role in the post-allo-HSCT setting, either as maintenance therapy or treatment of relapse. This was explored recently by Chen *et al.*[83] in a phase I trial of 22 patients with FLT3-ITD-positive disease who received sorafenib as maintenance therapy following allo-HSCT. In addition to establishing safety and feasibility, the authors of this study reported rates of PFS and OS which compared favorably to historical controls, particularly in the subset of patients in CR1 or CR2 at the time of transplant. In a retrospective analysis of six patients status post allo-HSCT, sorafenib as maintenance therapy ($n=5$) or treatment of relapse ($n=1$) resulted in a median PFS of 16 months, with all patients remaining in molecular remission (that is, FLT3-ITD-negative by PCR).[84] Interestingly, skin graft-versus-host-disease occurred shortly after initiation of therapy in five out of these six patients. In addition to its action as a TKI, sorafenib may therefore possess an immunomodulatory role, which synergizes with the graft-versus-leukemia effect.[85] Two phase I trials of sorafenib use in the peri-transplant setting are currently underway (NCT01398501 and NCT01578109).

Midostaurin. Midostaurin is another first-generation FLT3 TKI with significant but transient single-agent activity in patients with AML.[86,87] As with sorafenib, its effects are limited by the rapid emergence of resistance. Combinations of midostaurin and existing chemotherapy regimens are currently under investigation: results of a phase I and combined phase I/II trial of midostaurin and azacitidine have recently been published, demonstrating the tolerability and efficacy of this combination in patients with AML. In their cohort of 17 patients with a median age of 73, Cooper *et al.*[88] established a MTD level of 75 mg PO twice daily with no observed dose-limiting toxicities. In another phase I/II trial of the combination of midostaurin and azacitidine was tested in patients with AML (primary or secondary) and MDS, Strati *et al.* reported a lower MTD of 50 mg PO twice daily. The combination achieved an overall response rate of 26%, with median remission duration of 20 weeks. Although no DLT were observed in this study, neutropenia, thrombocytopenia and anemia developed in 96, 94 and 61% of patients, as well as infections and a decreased left ventricular ejection fraction in 56 and 11% of patients, respectively.[89] In a recent randomized, double-blind trial of 717 patients with previously untreated FLT3 (ITD and TKD) positive AML, Stone *et al.* explored the role of midostaurin in combination with a standard '7+3' induction regimen and high-dose cytarabine consolidation therapy. Patients randomized to the midostaurin treatment arm also received midostaurin as maintenance therapy for one year. Although no difference in the rate of CR was observed between the midostaurin and placebo arms, patients receiving midostaurin had a significantly higher OS and EFS (with a hazard ratio of 0.77 and 0.80, respectively).[90]

Quizartinib. Second-generation inhibitors such as quizartinib have been designed to specifically target the FLT3 kinase, in order to reduce toxicity from off-target effects. In addition to this increased selectivity, quizartinib also possesses a good bioavailability and a half-life of more than 24 h, which allows for a more continuous FLT3 inhibition. A phase I study of oral quizartinib in 76 patients with relapsed/refractory AML was able to achieve a hematological response in 30% of patients, and a CR in 13% regardless of FLT3 mutational status. Among patients with FLT3-ITD, the rate of hematologic response increased to 53%, with ~ 23% of patients achieving CR. Patients were able to tolerate doses of up to 200 mg/day, with grade 3 QT interval prolongation as the only DLT.[91] In one phase 2 trial, 137 patients with relapsed/refractory AML were given quizartinib monotherapy. The agent was administered in 28-day cycles at doses of 90 mg/day in females and 135 mg/day in males; the most common treatment toxicities were nausea and vomiting in 38 and 26% of patients, anemia in 29%, QT interval prolongation in 26%, febrile neutropenia in 25%, diarrhea in 20% and fatigue in 20%. The rate of composite CR (that is, CR, CR with incomplete platelet recovery and CR with incomplete hematological recovery) and the median OS were 34% and 25.6 months in FLT3-ITD-negative cases, and 44% and 23.1 months in FLT3-ITD positive cases. The observed benefit in FLT3-ITD-negative disease may be explained by off-target effects, or by the upregulation of the FLT3 TK pathway as suggested by the rise in FLT3 receptor ligand levels in patients receiving standard chemotherapy.[92] Once again however, the response to FLT3 TKI is limited by the rapid emergence of resistance: the median duration of remission was only 5 weeks in patients with FLT3-ITD-positive AML.[93] Interim analysis of a phase I/II trial of quizartinib in combination with azacitidine or cytarabine (NCT01892371) reported an overall response rate of 82% in FLT3-ITD-positive AML, MDS or chronic myelomonocytic leukemia.[94] A phase III trial comparing quizartinib monotherapy to salvage chemotherapy in relapsed and refractory AML (NCT02039726) is similarly underway.

Crenolanib. Crenolanib besylate is an orally available second-generation FLT3 TKI, with activity against FLT3-ITD and FLT3-TKD

mutants. Unlike other FLT3 TKIs, which are subject to the emergence of resistance conferring kinase domain mutations (such as D835Y), crenolanib appears to possess extensive 'pan-kinase' inhibition of secondary TKD mutations. Using concentrations far below the clinically achievable plasma levels, Smith *et al.* were unable to identify any single TKD mutation able to confer resistance to crenolanib.[95] In a phase II study of 38 patients with FLT3-mutated AML (including relapsed and refractory patients), crenolanib administered at doses of 200 mg/m^2 per day three times a day in 28 days cycle achieved a median EFS and OS of 8 and 19 weeks, respectively.[96] Crenolanib is currently being studied in multiple clinical trials in AML patients, both with and without FLT3-mutated AMLs.

STAT inhibitors

STAT3 tyrosine phosphorylation is upregulated in up to 50% of AML cases and confers a worse prognosis. Activation of the STAT3 signaling pathway is also stimulated by the FLT3 receptor ligand,[97] and may represent a key step in the development of FLT3 TKI resistance. Several small molecules of STAT3 inhibitors have been developed and are currently being investigated for the treatment of AML: in 2011, Redell *et al.* showed decreased STAT3 phosphorylation and induction of apoptosis in AML cell lines treated with the STAT3 inhibitor C188-9.[98] More recently, the optimized compound MM-206 demonstrated a dose-dependent induction of apoptosis in AML cell lines cultured in the presence of bone marrow stromal cells. The anti-tumor activity of MM-206 was confirmed *in vivo* by reducing blast count and improving survival in AML-engrafted mice.[99] OPB-31121 is a small molecule inhibitor of STAT3 and STAT5 phosphorylation, which has demonstrated activity in advanced solid tumors.[100] Treatment of various leukemic cell lines with this compound resulted in significant growth inhibition, including FLT3-ITD-positive AML cells.[101] Importantly, OPB-31121 was able to overcome FLT3 receptor ligand-induced STAT3 phosphorylation, and may help to prevent the emergence of resistance in patients receiving FLT3-ITD TKI. Other STAT3 inhibitors that work as antisense oligonucleotide (ASO) for STAT3 are in clinical trials in hematological malignancies including AML and will have to wait to see their efficacies in near future.

IDH1/IDH2 small molecule inhibitors

Gain of function mutations in IDH-1 and IDH-2 enzymes are found in approximately 20% of cases.[7] Recent attempts have been made to target these mutant enzymes as a potential treatment for AML. In 2013, Wang *et al.*[102] published the results of AGI-6780, a small molecule inhibitor of the R140Q mutant IDH-2 enzyme. In an *ex vivo* model of primary human AML cells, treatment with AGI-6780 was able to overcome the differentiation block of leukemic cells. Recently, the IDH-2 inhibitor AG-221 was found to confer a dose-dependent survival benefits in a primary human IDH-2 mutant AML xenograft model. At a cellular level, AG-221 treatment was associated with an initial phase of CD45+ blast cells proliferation, followed by cellular differentiation.[103] A phase I trial of AG-221 in IDH-2 mutant leukemia is currently underway (NCT01915498). IDH-1 mutant enzymes are also the targets of new therapeutic inhibitors: Preliminary results of a phase I trial of the small molecule inhibitor AG-120 (NCT02074839) demonstrated hematological response in 7 out of 14 IDH-1 positive patients, including 4 CR.[104]

Clofarabine

Clofarabine is a second-generation purine nucleoside analog approved for the treatment of relapsed or refractory pediatric acute lymphocytic leukemia. In AML, it has shown activity and tolerability as a single-agent, administered intravenously at doses of 20–30 mg/m^2 for 5 days, with overall response rates of ~40%.[105,106] In a 2008 randomized study of 70 patients aged 60 years and older, it was reported a CR rate of 63% using the combination of clofarabine with low-dose cytarabine, compared with 31% with clofarabine alone.[107] In a study of 320 patients over the age of 55 with relapsed/refractory AML, the combination of clofarabine and cytarabine achieved significantly higher rates of CR, CR with incomplete platelet count and DFS when compared with cytarabine alone.[108] Although neither of these studies was able to show an improved OS, these results suggest a synergistic action between clofarabine and cytarabine, and have spurred interest in the combination of these two agents. Recently a study was published showing the results of a phase 2 trial of clofarabine and low-dose cytarabine in older patients with newly diagnosed AML.[109] In this study, 118 patients age 60 or older (median age of 68 years) received induction therapy with clofarabine at 20 mg/m^2 on day 1 through 5 and low-dose cytarabine at 20 mg subcutaneously twice daily on day 1 through 10. In an attempt to improve survival, this was followed by consolidation and maintenance therapy with up to 18 cycles of clofarabine and low-dose cytarabine alternating with decitabine. CR was achieved in 60% of cases, with a median OS of 11.1 months, and a median RFS of 14.1 months. The regimen was well-tolerated, with a 4-week mortality rate of 3%. The most common non-hematological toxicities reported in this study included nausea in 81% of cases, elevated liver transaminases and bilirubin in 64 and 47% of cases, as well as rash in 56% of cases. Clofarabine may thus represent a well-tolerated addition to low-dose cytarabine in elderly patients unable to receive standard chemotherapy or allo-HSCT for consolidation therapy. Clofarabine has shown similarly promising results in younger patients when combined with the standard '7+3' induction regimen. In a study of 57 newly diagnosed patients under the age of 60, the combination of clofarabine (at 22.5 mg/m^2 IV daily for 5 days) with idarubicin and cytarabine used as a frontline induction and consolidation therapy achieved CR rates of 74% and a median EFS of 13.5 months (the median OS and RFS had not been reached by a median follow-up of 10.9 months).[110] A phase I/II study of frontline clofarabine, cytarabine and idarubicin in patients with intermediate and poor risk AML is currently underway (NCT00838240). The potential role of clofarabine in the peri-transplant setting is also currently under investigation. In a multicenter two-stage phase II trial, 84 patients with relapsed and refractory AML received clofarabine (at 30 mg/m^2 for 5 days) in combination with cytarabine as salvage therapy, followed by 4 days of clofarabine and one dose of melphalan in chemo-responsive patients with HLA-compatible donors. Out of the 56 patients who underwent allo-HSCT, CR was achieved in 50 (including 11 CR with incomplete platelet recovery and 10 CR by chimerism). The 2-year OS of 43% compared favorably with historical controls.[111] Although randomized controlled trials are needed to clearly delineate the role of clofarabine in AML these studies present promising results in support of this agent, particularly in combination with cytarabine in the elderly.

In addition to its activity as an intravenous agent, clofarabine has also captured interest as an oral agent for the treatment of AML. Unlike previous purine nucleoside analogs, clofarabine is able to resist acidic pH as well as phosphorolytic cleavage by gastrointestinal *Escherichia coli*. As a result it possesses a bioavailability of roughly 50%.[112] In a phase I/II study of 35 patients 60 years or older with relapsed/refractory AML or high-risk MDS the feasibility and efficacy of oral clofarabine combined with low-dose cytarabine was investigated as a first-line therapy.[113] At a MTD of oral clofarabine of 20 mg per day for 5 days, CR was achieved in 42% of patients (including CR with incomplete count recovery in 4%). Most importantly, more than 50% of cycles administered at the MTD were given in the outpatient setting. In a population at an increased risk of TRM, oral clofarabine may thus offer a valuable addition to reduced intensity chemotherapy.

Monoclonal antibodies

Monoclonal antibodies exert their anti-tumor activity through direct antibody-dependent cytotoxicity or through the conjugation of cytotoxic agents, which allows for the targeted delivery of potent chemotherapy to neoplastic cells. Gemtuzumab ozogamicin (GO) is a humanized recombinant antibody directed at CD33, a transmembrane protein expressed on cells of myeloid lineage. The antibody is conjugated to the DNA-cleaving cytotoxic agent calicheamicin, and is internalized by CD33-positive cells. GO received FDA approval in 2000 for the treatment of CD33-positive AML in patients 60 years or older at first relapse. However in 2009, interim analysis of a randomized clinical trial of 637 patients with newly diagnosed AML revealed increased fatal toxicity with no improvement in CR, disease-free survival or OS in patients receiving GO in combination with standard chemotherapy.[114] The trial was prematurely terminated and FDA approval was rescinded. Despite its removal from the market, a 2014 meta-analysis of five randomized clinical trials demonstrated a decrease in relapse and improved survival in patients receiving GO in addition to standard chemotherapy.[115] A subset analysis further revealed that this survival benefit was limited to patients with a favorable or intermediate cytogenetic-risk profile. Most recently, a randomized trial of 237 patients 60 years of age or older ineligible for intensive chemotherapy showed an improved OS (hazard ratio of 0.69) in those assigned to GO induction and consolidation compared with best supportive care.[116] This survival benefit was again most pronounced in patients with an intermediate to favorable cytogenetic-risk profile. Although further studies are required to fully delineate the effects of gemtuzumab in the treatment of AML, these data suggest a benefit among elderly patients with favorable or intermediate cytogenetic-risk profile. CD37 is a transmembrane protein that is expressed in high levels on maturing B cells. Although its exact function has not yet been elucidated, it is upregulated in non-Hogkin lymphoma and chronic lymphocytic leukemia.[117] Initially conceived as a therapy for B-cell malignancies, AGS67E is a fully human anti-CD37 IgG antibody that is conjugated with monomethyl auristatin E (MMAE), a potent microtubule-disrupting agent. AGS67E allows for the selective delivery of MMAE to CD37-positive malignant cells and results in apoptosis. Although CD37 is minimally expressed on normal myeloid stem cells it was recently demonstrated to have differential expression of CD37 on the surface of $CD34^+/CD38^-$ AML stem cells. *In vitro* treatment of leukemic cells with nanomolar concentrations of AGS67E resulted in cytotoxicity, altered cell growth and apoptosis in seven out of 16 AML cell lines. The administration of AGS67E was further found to significantly decreased tumor engraftment in a murine xenograft model of AML, resulting in undetectable leukemic cell levels in three out of four AML samples. CD37 may thus represent a novel therapeutic target for the selective inhibition of leukemic cell growth. Although still at an early stage of its clinical development, AGS67E is a promising new therapy. More importantly, the identification of unique molecular markers expressed on the surface of leukemic cells is an emerging avenue for the discovery of novel targeted therapies against AML.

CART therapy

Chimeric antigen receptors are synthetic T-cell receptors with antibody-like specificity. They combine a single-chain variable fragment from a monoclonal antibody with the transmembrane and intracellular domains of a T-cell receptor. This allows for the creation of a host-derived population of chimeric antigen receptor-T (CART) cells, which can be directed at a pre-determined antigen. CD19-directed CART cell therapy has shown exciting efficacy in the treatment of acute lymphoblastic leukemia and B-cell lymphoma. Although this treatment does not distinguish between malignant and healthy CD19 cells, patients tolerate the depletion of CD19 lymphocytes with relatively little morbidity. In contrast to this, depletion of the normal cells of myeloid lineage is associated with unacceptable neutropenia, and attempts to apply CART cell therapy to the treatment of AML have had to focus on identifying an appropriate antigen to target malignant cells while sparing non-malignant myeloid cells. Kenderian *et al.* recently developed a CD33-specific CAR based on the single-chain variable fragment of gemtuzumab ozogamicin. They have reported potent *in vitro* activity of such CD33-specific CART cells against AML cell lines.[118] CD33-specific CART therapy also prolonged survival in AML xenografts. However CD33 is expressed on normal cells of myeloid lineage and the reported anti-tumor effects were associated with profound cytopenias. Using electroporation of CD33-specific CAR mRNA into human T cells, the authors are able to induce the transient expression of anti-CD33 CAR,[118] which may confer clinically significant anti-tumor activity while avoiding long-term myelosuppression. In an attempt to selectively target leukemic myeloid cells, others have focused instead on the β member of the folate receptor family (FRβ). This receptor subtype is primarily expressed on myeloid-lineage hematopoietic cells, and is upregulated in the setting of malignancy.[119] FRβ is expressed in 70% of cases of primary AML, and its expression can be further upregulated following treatment with all-trans retinoic acid.[120] In a recent publication the effect of FRβ-specific CART cells therapy *in vitro* as well as in AML xenograft was reported. The study demonstrated lytic activity against FRβ positive AML cell lines both *in vitro* and *in vivo*. Importantly, no evidence of toxic activity against healthy human CD34-positive stem cells was observed *in vitro*.[121] Although still in its early stages, CART cell therapy may thus provide an alternative mechanism of treatment for patients with relapsed/refractory AML.

CONCLUSION

AML is a biologically and clinically heterogeneous disease. Although advances in supportive care and prognostic risk stratification have optimized established therapies, overall long-term survival remains poor. Elderly patients who account for the majority of newly diagnosed cases are more likely to present with an adverse cytogenetic profile. At the same time the increased risk of TRM often precludes this population of patients from receiving optimal chemotherapy or stem cell transplantation. Novel targeted therapies offer the promise of effective anti-leukemic activity with reduced toxicity from off-target effects. However given the molecular diversity of AML, it is unlikely that targeted therapies such as FLT3 tyrosine kinase inhibitors will provide a single 'magic bullet' against this disease. Rather the development of new treatments, in concert with improved genetic profiling and risk stratification, can be expected to result in incremental gains in remission and survival. Furthermore in addition to mutated enzymes and upregulated pathways, the identification of unique cell surface markers can provide a therapeutic target for recombinant monoclonal antibodies or chimeric antigen receptors. Here, the challenge lays in selectively targeting leukemic myeloid cells while sparing non-malignant myeloid precursors. Lastly, the development of well-tolerated oral therapies, such as clofarabine, will increasingly broaden the range of available treatment for elderly patients at a higher risk of mortality from standard chemotherapy regimens. We are looking to a new era in the treatment of AML to begin with novel agents so we can achieve better responses with prolong OS particularly for patients with relapsed or refractory diseases and poor cytogenetic features.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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